ANAPHYLAXIS

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ANAPHYLAXIS

BY

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MEDICAL REGISTRAR TO THE LIVERPOOL ROYAL INFIRMARY

WITH A PREFACE BY

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PREFACE

In the progress and development of the Science and Art of Medicine, and of the kindred pursuits of Physiology and Pathology, successive investigators find themselves confronted with facts and with difficulties of which their predecessors were unaware, or whose significance and importance they overlooked. The more closely the phenomena of life, whether in health or disease, are examined, the more complex they are found to be; the attempt to solve the problem of yesterday has ended in the statement of the problem of to-day.

To the philosophical thinker the physiology, the pathology, and the medicine that dealt mainly with the physical and mechanical properties of the living organism were unsatisfying, inasmuch as they largely ignored the essential phenomena which distinguish living sentient beings from inert matter; while dealing with the grosser manifestations of life in health and disease they hardly touched on the specific essential properties on which these manifestations must be assumed to depend.

During the last quarter of a century, however, the labours of the cytologist, the bacteriologist, and the biochemist have thrown a flood of light on the intimate processes of life, and the physician has not been slow to endeavour to turn to practical account the suggestions they have offered for his guidance.

Not the least important of the advances in medicine which have taken place on these lines have been the introduction into practice of organo-therapy, and the administration of serums and the so-called vaccines; lines of treatment which, though by no means universally or even widely applicable, have been found to yield remarkable, indeed brilliant, results in certain forms of disease.

It would not be surprising, still less would it be any just ground for rejecting the aid of these newer methods of treatment, if experience should show that their employment is not unattended with certain inconveniences, amounting perhaps to a slight degree of risk. Such has been the case with every substantial advance in therapeutics. A few years' experience of antiseptic surgery sufficed to show that the system as at first carried out was attended with serious disadvantages, and even dangers ; none the less the surgeons who had faith in it continued to employ it, the dangerous elements were found to be non-essential to the method and means were found by which they were eliminated.

The present work is a clear and able exposition of certain striking, often alarming, phenomena which, in the opinion of the author and of others who have worked on similar lines, may be expected to follow the introduction into the organism, at long intervals, of successive doses of albuminous substances such as are employed in some of the modern methods of treatment already referred to. To what extent, if at all, they constitute a real danger in the employment of such medication no definite opinion is generally held ; that they may constitute a danger is a possibility that is deserving of serious consideration ; but, on the other hand, if they do there is no valid reason to doubt that the danger depends on some contingent element in the method, and that means will be found to eliminate it without impairing the efficacy of the remedy.

Dr. J. Murray Bligh has made a special study of the question of anaphylaxis, he has made himself fully acquainted with the views of Professor Richet on the subject, and he has performed numerous experiments with a view to making himself familiar with the phenomena in question. He will no doubt before long be in a position to add some of the results of his observations to the literature of the subject; but in the meantime he considers that the time is ripe to insure for the medical profession in English-speaking countries a more general acquaintance with the teachings of Professor Richet than it is likely to obtain until an authoritative work on the subject appears in the English language. He has therefore undertaken the task of translating Professor Richet's work on Anaphylaxis into English, he has accomplished it with great success, and he offers it to the members of the medical profession in English-speaking countries in the hope that it will be effectual in bringing more closely to their notice the important and fascinating subject with which it deals.

THOMAS ROBERT BRADSHAW.

LIVERPOOL, *March* 1913.

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ANAPHYLAXIS

CHAPTER I

HISTORICAL

Anaphylaxis is the opposite condition to protection (phylaxis). I coined the word in 1902 to describe the peculiar attribute which certain poisons possess of increasing instead of diminishing the sensitivity of an organism to their action.

The first article containing a detailed description of the main phenomenon appeared on February 15, 1902.[1] In it this fact, the very basis of anaphylaxis, was stated, that a substance which neither killed nor sickened a normal animal, gave rise to intense and fatal effects in an animal which some time previously had been given a dose of the same substance.[1]

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[1] P. Portier and Ch. Richet, "The Anaphylactic Action of Certain Poisons" (*Bulletin of the French Biological Society*, 1902, pp. 170-2).

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[1] The experiments and deductions which led to the discovery of the phenomenon may be briefly stated here.

During a cruise on Prince Alfred of Monaco's yacht the Prince and G. Richard suggested to P. Portier and myself a study of the toxic properties of the Physalia found in the South Seas. On board the Prince's yacht experiments were carried out, proving that an aqueous glycerin extract of the filaments of Physalia is extremely toxic to ducks and rabbits. On returning to France I could not obtain any Physalia, and decided to study comparatively the tentacles of Actinaria, which resemble Physalia in certain respects, and are easily procurable. Owing to the kindness of Y. Delage I was able to obtain a large quantity; the tentacles, cut close to the body, were placed in glycerin, and thus we had in Paris several litres of an intensely toxic fluid, the glycerin dissolving and extracting the active principle.

While endeavouring to determine its toxic dose we soon discovered that some days must elapse before fixing it; for several dogs did not die until the fourth or fifth day after administration, or even later. We kept those which had been given a dose insufficient to kill, in order to carry out a second investigation upon them when they had completely recovered.

At this point an unforeseen event occurred. The dogs which had recovered were intensely sensitive, and died a few minutes after the administration of small doses. The most typical experiment, that in which the result was indisputable, was carried out on a particularly healthy dog. It was given at first 0·1 c.c. of the glycerin

In this paper we showed that *accumulation* is not the cause; for at the end of three, four, or five days there is no anaphylaxis: at least two or three weeks must elapse before it appears.

These two factors—(*a*) increased sensitivity to a poison after previous injection of the same poison, and (*b*) an incubation period necessary for this state of increased sensitivity to develop—constitute the two essential and sufficient conditions for anaphylaxis.

It will be seen later how severe the phenomenon may be and how far it is possible to demonstrate it. But it is hardly surprising that incidents resembling anaphylaxis, observed before its formal verification, are scattered through-

extract without becoming ill; twenty-two days later, as it was in perfect health, I gave a second injection of the same amount. In a few seconds it was extremely ill; breathing became distressful and panting; it could scarcely drag itself along, lay on its side, was seized with diarrhœa, vomited blood, and died in twenty-five minutes.

out various contributions to physiology and experimental pathology.

In 1839 Majendie observed that while rabbits easily tolerated a first injection of albumin, they could not, some days later, tolerate the injection of a similar dose. Flexner in 1894 proved that rabbits surviving a first injection of dog serum without a symptom, died some days or weeks later, when given an equal or even smaller dose.

But it was above all in Koch's memorable experiments with tuberculin that the phenomenon of supersensitivity to a special poison was particularly demonstrated (1890). To-day every one is convinced that here is a true anaphylactic phenomenon, though, as will be seen, definite proof of it has not yet been given; for, in the first place, the state of a tuberculous animal cannot exactly be compared with the state of an animal which has received an injection of antigen, and, in the second, tuberculin itself does not act like a true antigen. Accurate studies of these points have not yet been completed.

Behring, in 1893, studying the effects of diphtheritic toxin on guinea-pigs, showed that these animals, once injected with this toxin, become, in certain cases, more intensely sensitive to it, but he did not consider the phenomenon either general among the injected animals or common to all poisons. Studying immunity particularly, he considered supersensitivity a *paradoxical reaction.*

Knorr and Kitasato, working under his direction, showed that in some instances guinea-pigs died after doses 700 or 800 times weaker than the fatal dose. But these workers neither stated the general principle nor the circumstances of the phenomenon they had incidentally observed in the course of their earlier admirable studies of immunity.

In 1894 Aducco published a paper entitled "Intensified Action of Cocaine on Repetition of its Administration after a Short Interval." As, in his experiments, intensified action meant more rapid rise of temperature with convulsions, and in addition too few days passed between the first and the second injection to admit of certainty that it was not a phenomenon of accumulation, he does not claim that this supersensitivity is explainable, otherwise than by the accumulation of cocaine in the organism. It is highly probable that in this instance there was no question of true anaphylaxis.

In 1894 Arloing and J. Courmont (quoted by P. Courmont, *Summary of General Pathology*, 1908, p. 191) noted that successive injections into man of donkey serum produced toxic effects.

In 1898, while studying with J. Hericourt the effects of eel serum on dogs, I noticed that the second, and more markedly the third, injection made them sick and waste away. But I must admit I did not understand the significance of this result, and contented myself with supposing there was increased sensitivity without attempting to analyse the phenomenon thoroughly.

P. Courmont in 1900 stated that on inoculating guinea-pigs with successive and very weak doses of the effusion of tuberculous pleurisy, the animals died before receiving a quarter of the total dose they took easily as a single injection.

Thus, before my experiments with the virus of Actinaria were made, the only precise scientific idea relative to the sensitivity of animals to second injections was that *sometimes* some animals, instead of being immunised by first injections, were sensitised, and that *sometimes* animals whose blood contained large quantities of antitoxin succumbed to weak doses of toxin.

Before dealing with the actual study of anaphylaxis I will mention the leading principles laid down in my papers of 1902.

1. A definite incubation period is necessary before anaphylaxis can be induced.
2. The anaphylactic state lasts many weeks.
3. There may be some similarity between anaphylaxis and immunity.
4. Anaphylaxis is to a certain extent specific; that is to say, the second injection should be of the same nature as the first.
5. The symptoms of anaphylaxis are immediate and intense, while the symptoms of primary intoxication are mild.
6. The anaphylactising substance is thermostable.
7. The anaphylactising toxin affects the central nervous system, and

the essential phenomenon is a disorganisation of this system, with a considerable fall in the arterial blood pressure.

The work of various experimentors from 1903 to 1910 has enormously extended the field of anaphylaxis.

I will briefly mention the chief results.

1. Several primary injections of normal serum into an animal develop an anaphylactic state. A toxin is not required, therefore, to create anaphylaxis. Anaphylaxis follows the injection of non-toxic and harmless substances; it is alone necessary that they be of an albuminoid nature (Arthus, 1903).
2. Accidents observed in man, following injections of serum, are anaphylactic phenomena (Pirquet and Schick, 1903).
3. A single injection of antitoxic serum leads to anaphylaxis on a

second injection of normal serum, even if the second dose is extremely small (Theobald Smith, 1906), even as much as 0·00001 c.c. (Rosenau and Anderson, 1906). Normal serum has exactly the same effects in first injections as antitoxic serum (Otto, 1906).

4. It is possible by intercurrent injections to prevent the appearance of the anaphylactic state (Otto, 1906). This is anti-anaphylaxis (Besredka and Steinhardt, 1906).
5. Animals inoculated with a known micro-organism are, in a definite and specific manner, anaphylactised to the toxin of this micro-organism.
6. The specificity of anaphylaxis is so precise that it is possible for the purposes of forensic medicine to determine, by the presence or absence of an anaphylactic reac-

tion, the type of animal whose blood has been injected, although an extremely weak dose was administered (Rosenau and Anderson, 1907; Besredka, Uhlenhuth, 1909).

7. There is a form of anaphylaxis termed *passive;* that is to say, the blood of anaphylactised animals injected into normal animals produces anaphylaxis in them after a large number of injections (Nicolle, 1906), occasionally *after a single primary injection* (Ch. Richet, 1907).
8. Anaphylaxis may be produced by mixing *in vitro* the serum of anaphylactised animals with antigen, and injecting the mixture into normal animals (Ch. Richet, 1907).
9. There is a definite relationship between the production of the anaphylactising toxigen, the for-

mation of precipitate, and the deviation of the complement (Friedberger, 1909).

10. Animals sensitised by anaphylactising substances are, to a certain extent, sensitised to all poisons, even crystalloids (Ch. Richet, 1910).

These are the main points established between 1902 and 1910. In the course of this work the actual experiments on which the definite theory of anaphylaxis is established will be pointed out.[1]

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[1] Although this is intended to be a summary of the work on anaphylaxis to date, I may be allowed to include a number of facts observed by myself and as yet unpublished.

CHAPTER II

DEFINITION OF ANAPHYLAXIS

As a result of the injection of a toxic substance into several animals of the same species a variable and individual effect can always be demonstrated. Some are very resistant, others intensely sensitive. Must the cases of susceptibility be considered instances of a spontaneous anaphylaxis?

The point is of importance, more especially as in medical practice analogous cases are met with which are considered as phenomena of idiosyncrasy. It has long been known that some people after eating shell-fish, mussels, or strawberries are liable to erythema, urticaria, and indigestion, with nausea and syncope; all these are phenomena having characteristics strongly resembling those of anaphylaxis. In such people very small quantities of the ingested substance produce marked symptoms, while in the majority of people the results are those of normal food, and no symptoms are produced.

The fact of anaphylaxis by ingestion is definitely proven. But it is probably not sufficient to account for those individual differences observed after the injection of substances which certainly were not present in the food of the sensitive individuals.

Let me give two examples. A bitch having received 0·0051 gramme per kilo of crepitine, a dose which is fatal only at the end of ten days and never produces an immediate effect, suddenly became extremely ill, vomiting, passing bloody motions, and dying within twenty-four hours. Another bitch (unpublished experiment), which received an extremely small dose of warmed crepitine, immediately became ill, vomiting and passing bloody motions, and dying the same night. These are instances of a peculiarly definite and strictly individual susceptibility.

Similar facts, although very rare, have been observed by G. Sobernheim among some thousands of cattle treated with anti-anthrax serum. Some animals which had not received a preliminary injection of a substance, whatever it might be, were, especially after the first injection, extremely ill, with œdema of the snout and eyelids, profuse nasal catarrh, and general disturbance.

This abnormal individual supersensitivity of some animals may be compared with the intense sensitivity of certain human beings to sero-therapeutic injections.

Landouzy called attention to the hereditary transmission of predisposition to tuberculosis. Tuberculosis itself, so far as it is a microbic infection, is not in question. He considers solely the increased susceptibility to infection which is present in the children of tuberculous parents. In these children there is an increased sensitiveness to infection, directly due to modification of disposition, and this predisposition may be associated with a kind of anaphylaxis. His opinions on this subject, presented to the Brussels Congress on Tuberculosis (1910), are highly important, and suggest a comparison between anaphylaxis and heredity. Here is an entirely new and unexplored field, suitable for experimental as well as clinical investigation.

It does not seem to me, however, that we are fully justified in comparing such facts with anaphylaxis; if we do, where is a line to be drawn? Since, obviously, the effect of a given poison on different individuals cannot be the same, the real differences between individual susceptibility and true anaphylaxis cannot be strictly defined. This difficulty arises in all questions concerning which it is desirable to be accurate and to understand completely. It is impossible to give limitations.

Doubtless anaphylaxis can be inherited. But this appears to be only a special instance of passive anaphylaxis. It has been demonstrated, but does not seem to be of long duration.

Rosenau and Anderson showed :

1. That hereditary transmission is a function of the mother, and not of the father. Ehrlich noticed this same fact in connection with the immunity conferred by castor-oil.
2. That anaphylaxis is not transmitted by the milk.
3. That anaphylaxis can be produced before or after conception.

So that we may consider hereditary

anaphylaxis as an example of passive anaphylaxis. Otto observed that it is quite definite in the guinea-pig, that it remained very definite up to the forty-fourth day after birth, but that towards the seventy-second day it entirely disappeared, which would not be the case were it a question of active anaphylaxis.

In conclusion, let it be stated that, besides cases of anaphylaxis by alimentary absorption and hereditary anaphylaxis, there are certain instances of exceptionally marked individual susceptibility which we have no right, as yet, to include in the term anaphylaxis. Indeed, it is possible by physiological methods to modify the reactions of an animal in such a way that immediately after the injection of a poison it reacts just like an anaphylactised animal. I have induced this condition by means of profuse hæmorrhage. A dog which had been bled 4·3 per 100 of its weight (never fatal in a dog) was given 0·001 c.c. of crepitine, an amount never fatal in a normal dog even at the end of a month. Immediately its condition became miserable, resembling that of an anaphylactised dog. Here it would be absurd to speak of anaphylaxis; rather is it an instance of increased sensitivity for which the previous hæmorrhage may be held responsible. It is clear that in certain states which we do not understand some individuals are more sensitive, although there is no question of spontaneous anaphylaxis.

CHAPTER III

THE INCUBATION PERIOD

It is impossible to fix accurately the duration of the incubation period; it depends upon the dose, upon the type of animal, and especially upon the nature of the antigen used. It may be stated, however, that without exception some time must elapse before anaphylaxis appears. Lewis obtained it as early as the sixth day by injection into the heart. Rosenau and Anderson observed that during the first six days following the injection of horse serum into guinea-pigs there were no phenomena following a second injection; from the seventh to the tenth day their intensity increased. After the fourteenth day the anaphylactic reaction reached its maximum. Further, the incubation period is not altered by the amount of the dose or by the site of injection, which may be into the brain or under the skin.

With mytilo-congestine, actino-congestine, and crepitine the incubation period appears to me to be variable. Dogs that have been given an intra-venous injection of mytilo-congestine may be anaphylactised on the tenth day. But the maximal reaction is not obtained until the fifteenth day. Anaphylaxis from actino-congestine only appears on the twelfth day, the slowly developing maximal reaction not being obtained until the twenty-eighth day. Anaphylaxis from crepito-congestine commences later still. Before the twenty-eighth day there is practically no reaction, and it scarcely reaches its maximum before the thirty-sixth day. These differences in the incubation period of anaphylaxis to these three poisons correspond pretty well to the differences between the duration of their toxic action. Death from mytiline poisoning occurs on the fourth day, from actine poisoning on the seventh day, from crepitine poisoning about the fifteenth day, in dogs as well as in rabbits and guinea-pigs.

As second injections of serum in man, and more particularly in children, lead to accidents never occurring after first injections, the duration of the incubation period of anaphylaxis demands careful consideration. According to Pirquet, a second injection, given five or six days after the first injection, leads to phenomena of local anaphylaxis, but the maximal effect is only produced after the twelfth day. According to Arthus, the anaphylactic state in the rabbit, following injections of horse serum, only commences on the eighth day. It is then very slight. He does not consider that the amount of the first dose has any great influence. According to other authors, the amount of the first dose has some influence over the duration of incubation. After very weak doses, Otto has never seen anaphylaxis before the eleventh day. Gay and Southard have observed it on the fourteenth day; Otto on the seventeenth; Besredka on the twelfth day.

First injections of large doses have an effect such as might have been anticipated. They shorten, rather than prolong the incubation period. If about the sixth day after the first injection a second injection, and then a third are given, the onset of anaphylaxis is delayed. It would seem that anaphylaxis only follows the complete disappearance of the antigen from the blood. As will be seen later on, both the antigen and toxigen cannot be present simultaneously in the blood. Consequently the toxigen appears slowly after a very large dose of antigen.

Finally, incubation periods are only comparable in those cases in which the second injection has been introduced through the same channel as the first, as Otto, Gay, Southard, Rosenau and Anderson have noted. For example, a guinea-pig which on the tenth day is sensitised for a second injection to be given intracardially will not react to a second injection given subcutaneously.

It is impossible, therefore, to lay down any definite rule ; but it may be stated that the shortest incubation period for anaphylaxis is ten days.

From the tenth to the twentieth day the intensity of the anaphylactic state increases, reaching its maximum towards the twentieth day, and, in certain cases, with certain antigens, towards the fortieth day.

CHAPTER IV

THE DURATION OF ANAPHYLAXIS

Anaphylaxis lasts a considerable time. As yet its limitations are unknown. In 1903 I pointed out that it is possible to demonstrate it at the end of a year, and since then I have proved that it is even more lasting. Rosenau and Anderson, in particular, demonstrated this important fact. They cite an instance of a guinea-pig retaining its sensitivity to a second injection, 1096 days, just over three years. They add, "*We believe that sensitised guinea-pigs retain their susceptibility during their entire life.*" Currie reports a case, in a man, in whom anaphylactic effects manifested themselves on a second injection, 1817 days after the first (quoted by Doerr).

Not only does the anaphylactic state persist, it does not even appear to diminish, though, after the injection of certain antigens, considerable differences become manifest.

After a first injection of mytilo-congestine, the anaphylactic state completely disappears about the fortieth or fiftieth day; but it does so only apparently, for the phenomena are complex. Coincident with the development of anaphylaxis, immunity appears, and this inevitably masks some of the symptoms of anaphylaxis, possibly on account of some antitoxin immediately neutralising the effects of the toxin by simple chemical reaction.

Anaphylaxis induced by other poisons does not disappear so quickly. Rosenau and Anderson did not observe any appreciable weakening on the hundredth day after the first injection. With actino-congestine, I observed on the one hundred and thirty-fifth day (Laboratory

Reports, 1909, vi. 449) the most intense anaphylaxis I have ever seen, the animal dying fifteen minutes after an injection of a tenth of the fatal dose. With crepitine the symptoms on the ninety-second day have been among the most intense. It would appear, too, that in dogs, when a very long period has elapsed since the first injection, the symptoms are more serious than those developing about the fiftieth day. Possibly they take a slightly different form, with tonic and clonic convulsions and rapid death (unpublished work).

During the period between the first and second injection, can it be said that the animal returns to its normal state?

About the tenth or fifteenth day after the injection of serum into rabbits and guinea-pigs, the appetite returns, they attain their former weight, and soon begin to increase it.

Horse serum is only toxic in very large doses; it may almost be said not to be toxic. Arthus was able to inject 50 c.c. of horse serum into rabbits without any effect; so that it is not surprising that animals recover rapidly after such an injection. It is otherwise in rabbits, dogs, and guinea-pigs injected with a very strong anaphylactising toxin. Such a toxin occasionally has lasting effects; for example, crepitine, a vegetable albuminous extract of *Hura crepitans*, so alters nutrition that at the end of three months the animal still shows the effects of it; in general, dogs on which I have experimented do not completely regain their former weight. But they cannot be distinguished from normal dogs as far as liveliness and apparent good health are concerned.[1] Certainly there are a few easily-appreciated alterations; for example, there is always a definite leucocytosis. At the end of six months dogs injected with crepitine have 18,000 leucocytes per c.m., instead of 10,000, the normal figure.

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[1] M. Villaret and Faure Beaulieu, in my laboratory, endeavoured to find morphological changes in the central nerves and in lymphatic glands following the first intoxication by anaphylactising toxins. Their results were negative.

The persistence of the anaphylactic state during so long a period is one of the most remarkable phenomena in biology, and it is certainly one of the essential factors of individual differentiation. The fact of previous intoxications by means of any substance whatsoever, even if the intoxication has been slight and the effects have completely disappeared, places an individual in a special state which differentiates him from all other individuals of the same species. It is well known that an immunised individual is no longer the same as a non-immunised individual. Here likewise a new difference appears; an anaphylactised individual is no longer the same as a non-anaphylactised individual. Even alimentary ingestion, by the absorption of certain albuminoids, or microbic infections, by the production of toxins in the blood and tissues, may produce anaphylaxis and immunity.

Partly as the result of the food that has been taken, and partly as the result of multiple microbic infections which have attacked him and most often pass unnoticed, each individual is profoundly different from his neighbour, each has been prophylactised or anaphylactised to different degrees against different substances. Each is himself, and not another. Each has his idiosyncrasies, or, to put it better, his humoral individuality, as well as his psychological individuality, to differentiate him. Previous impressions, so variable in different persons, render each person's intelligence peculiar and personal. In the same way humoral impressions, if such an expression is permissible, induce in each individual a humoral personality just as characteristic of him as his intellectual personality.

CHAPTER V

SYMPTOMS OF ANAPHYLAXIS

ANAPHYLAXIS has been studied both by physicians and by physiologists. The symptoms in man and in animals, although essentially the same, are not absolutely identical. Moreover, in different animals it appears with varying characteristics.

Physiologists have experimented chiefly on the guinea-pig, the animal of choice for anaphylaxis. Arthus has studied it in the rabbit. I have analysed its effects particularly on the dog, in which, more easily than in any other animal, it is possible to dissociate the various phenomena from one another.

A.—Anaphylaxis in the Dog

Mild anaphylaxis is distinguishable from profound anaphylaxis, and the various stages between the mildest forms which are scarcely appreciable and the gravest forms which kill in a few minutes are likewise distinguishable.

In the mildest forms, the only symptoms are pruritus, increase in the number of respirations, lowering of the arterial pressure, increased frequency in the movements of the heart, diarrhœa, and tenesmus.

Of course some of these symptoms may be absent. Pruritus is only observed in cases of mild anaphylaxis; it will not develop if the nervous system is seriously affected. In order to observe it, the dog should be let loose. It will be seen to sneeze, and shake its head repeatedly, as if its ears were irritated; later, it scratches its head and sides sometimes furiously, rubs its muzzle on the ground and rolls there.

A more constant phenomenon than pruritus is increased frequency in the respirations, which, without amounting to asphyxia or dyspnœa, as in the more serious forms, proves by the change in rhythm and in amplitude that the poison has taken effect upon the central nervous system.

The arterial pressure is lowered, more or less, according to the general intensity of the reaction, and there is intestinal congestion. This early lowering of the arterial pressure, which in 1902 I pointed to as the criterion of the anaphylactic reaction, has been observed since by all physiologists, by Arthus in his studies of sero-anaphylaxis in rabbits, and by Biedl and Kraus more recently.

This may be explained by assuming that the result of anaphylaxis is a paralytic vaso-dilatation in the intestines, which naturally leads to lowering of the arterial blood pressure and acceleration of the heart. Besides, the same effects manifest themselves in anaphylactised animals which have received atropine, so that evidently it is not the heart, but the peripheral vaso-motor system, especially that of the intestine, upon which the anaphylactic poison acts.

All these symptoms rapidly disappear in cases of mild anaphylaxis. But if anaphylaxis is profound, they assume a very different aspect. In this case there is no pruritus. The earliest effect, the first symptom, is frequent vomiting, so prominent that in a number of cases it develops at the end of ten seconds or almost immediately after the injection even of a very small dose. This vomiting is so characteristic that I have taken it as a criterion more easy to observe than the fall in blood pressure. It may be said that it is never absent except in some very rare cases of extraordinarily intense anaphylaxis. In these the animal is immediately in such a state of prostration that it has no strength to vomit. The vomit is frothy and mixed with bile ; sometimes it is fæcal, and sometimes, in the severest cases, mixed with blood : for, from the beginning, there is an intense gastro-intestinal congestion.[1]

As soon as the animal is set free, it is seized with tenesmus and there is fluid diarrhœa mixed with blood. Sometimes practically pure blood is evacuated from the rectum, and this may be accompanied by severe colic.

But frequently the outburst of nervous symptoms is so sudden and so violent that the colic and diarrhœa never appear. Ataxia rapidly supervenes ; the animal staggers as if it were intoxicated ; it becomes paraplegic, drags the hinder part of its body, and does not raise the toes of its fore-paws, thus resembling those animals whose rolandic convolutions have been destroyed. The pupils dilate and the eyes are dulled, while the animal passes urine and fæces, becomes exhausted and insensible, and fails to respond to any reflex stimulations, and assumes a state of complete mind-blindness. Respiration is quickened and dyspnœic; the arterial pressure is very low, scarcely 4 to 5 c.m. of mercury. The heart hurries its beats, which are so weak that sometimes they can scarcely be counted. Fæcal matter, fluid, diarrhœic, and blood stained, pours from the rectum without the animal perceiving it. Breathing soon becomes so harassed that death from asphyxia seems impending. The general condition is serious enough to believe death imminent, but in reality death in less than two hours is extremely rare in the dog. Besredka has rightly called this sudden alteration of the nervous system *anaphylactic shock.*

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[1] The experiments were made on animals fasting for twenty-four hours, so that the stomach was always empty.

In most cases, if the second injection is not too strong, the dog recovers quickly. At the end of twenty to forty minutes, rarely longer, it suddenly rouses itself, moves, and takes a few staggering steps; it regains consciousness and sensibility, and although diarrhœa and tenesmus persist, it appears almost well. But in some instances it cannot get up, and dies at the end of three, four, five, or six hours, rarely within one or two hours, with an intense hæmorrhagic diarrhœa, without having risen from the spot where it collapsed.

I have already stated that in some very exceptional cases there are twitchings and convulsions.

Even when the dog has recovered from the anaphylactic shock, and has managed to reach its kennel, it may die during the night from persistent intestinal hæmorrhage and consequent enfeeblement.

In certain other cases it may die of chronic anaphylaxis on the second or third day. This possibly may be owing to the intestinal lesion which is the direct result of the hæmorrhage, or because there are serious and irreparable lesions such as congestions and hæmorrhages in the central nervous system.

Coincident with acute anaphylaxis, gastro-intestinal hæmorrhage occurs, chiefly intestinal, the whole intestine being filled with blood. A large quantity of blood is left in the intestines, which is more or less quickly reabsorbed, but reabsorption is accompanied by serious symptoms, forming a kind of general hæmatic, humoral, and non-microbial infection. All the tissues are yellow in colour, as in some forms of hæmatogenous jaundice. Loss of appetite persists and food is not digested. The intestinal mucosa does not recover its function for a long time. In other words, death from chronic anaphylaxis is due to a complication of acute anaphylaxis, namely, intestinal hæmorrhage, the intensity of which controls the progress of chronic anaphylaxis.

As to the cause of death in acute anaphylaxis, in the dog at any rate, it seems to be the result of asphyxia due to pulmonary congestion. To asphyxia is added internal hæmorrhage, or, at least, an intense congestion of the whole vaso-motor system of the intestines. The pulmonary circulation becomes more and more embarrassed, the blood circulating under very low pressure, so that the central nervous system is not efficiently supplied, and death results from inefficient hæmatosis.

At all events it is clear from an analysis of the symptoms that the anaphylactic poison which we shall call *apotoxin* poisons the central nervous system, as I pointed out in 1902. Everything is indicative of this: the immediate vomiting, the ataxia and vertigo, the dilation of the pupil, the mind-blindness, and the vaso-motor paralysis. Apotoxin acts upon the medulla and the highest nerve centres, which, in all cellular organisms, are well known to be the most sensitive to the action of poisons.

Three points have still to be noted: (1) When a profound anaphylactic state is established the symptoms cannot be intensified by increasing the second injection three times, five times, or even ten times. If, after an injection of 10 c.c., severe symptoms follow, 50 c.c. or even 100 c.c. of the same fluid can be injected without any alteration in the progress of the phenomena. Often, after the administration of a weak dose, which has induced violent anaphylactic shock, during which a much stronger dose is given, the animal recovers and lives: (2) Whatever the antigen injected may be, if the second dose is of the same nature it induces anaphylactic symptoms, and these symptoms are practically the same. Whether mytilo-congestine, suberitine, actino-congestine, or crepitine be used, the same group of organic reactions always appears, so that one is tempted to think that the same terminal poison *apotoxin* is invariably produced: (3) The onset of the anaphylactic phenomena is sudden, developing in a minute, sometimes in half a minute, sometimes even during the actual injection; it is very rarely that the maximal effects occur later than the sixth or eighth minute. Likewise the animal, which appears very ill and dying, revives suddenly, and completely recovers from the severe attack it has just survived.

Arthus has seen in the rabbit this

sudden return to the normal state which I have distinctly seen in the dog; Kraus and Doerr have seen it in the guinea-pig.

To prove more emphatically that the anaphylactic toxin affects the nervous system, an important experiment was suggested to Besredka by Roux, which, though it has been carried out on the guinea-pig, may be mentioned here. By anæsthetising a guinea-pig with ethyl oxide or ethyl chloride or chloral the anaphylactic shock is inhibited, and the *animal awakens vaccinated.* Moreover, anæsthetics have the general property of suppressing all nervous intoxication, probably because the chemical action of the anæsthetic on the nerve-cell prevents the protoplasm of the neuron from entering into any other chemical combination. It is well known that chloralised animals can bear large doses of strychnine without convulsions (Vulpian). If the dose is a fatal one, they die; convulsions ensuing as the chloral is eliminated. I have repeated this experiment with ammonium salts, which are convulsionary, and with veratrine, which is both convulsionary and emetical. Chloralised animals did not vomit when injected with veratrine, nor were they convulsed when injected with ammonium salts. We will consider this experiment again when discussing later the theory of anaphylaxis.

All workers have not obtained similar results. Rosenau and Anderson, experimenting on the guinea-pig, observed that urethane, given by the mouth, does not prevent death after the administration of the second injection, although there was complete narcosis. Practically the same result was obtained after a previous injection of chloral. Of eleven anaphylactised and chloralised guinea-pigs, six died; whilst of five normal and chloralised guinea-pigs, there was only one death; neither paraldehyde nor magnesium sulphate had any action. Nevertheless it must be said that these experiments of Rosenau and Anderson are not altogether negative, firstly because the anæsthesia was not absolutely complete, and secondly because a certain number of their anaphylactised guinea-pigs (45 per cent.) survived, when they should have died from the effects of the second injection.

The blood certainly undergoes important chemical changes; but their nature is unknown to us. We are only acquainted with its morphological changes.

I have noticed a considerable leucocytic reaction in anaphylactised animals. It is possible to distinguish it from that observed in animals injected for the first time, and to prove that in the anaphylactised animal the reaction, even to doses ten times weaker, is three or four times stronger. For example, if 0·0015 c.c. of crepitine be injected into a dog having 10,000 leucocytes per cubic millimetre, a leucocytosis of 30,000 will develop. It will still be 15,000 at the end of two months. But on giving the second injection, producing serious anaphylactic symptoms, there will develop a leucocytosis approaching 90,000 per cubic millimetre.

It would be unwise to attribute this leucocytosis definitely to anaphylaxis; for the animal is immunised at the same moment as it is anaphylactised, and it is unknown to which of the two the leucocytosis should be attributed. However, as the second dose injected is much weaker, and as the leucocytosis is much greater than that after the first dose injected, the supposition that immunity is the cause can in all probability, though not with certainty, be discarded; for it is in no sense absurd to imagine that an immunised animal reacts, from the point of view of leucocytosis at least, more rapidly and more intensely than a normal animal. Up to the present it does not seem possible to attribute the leucocytosis to anaphylaxis with certainty; at the most it can only be declared that very well marked leucocytosis coincides with a very severe anaphylaxis.

Arthus (*loc. cit.* 487) has also observed a marked leucocytosis in chronic anaphylaxis in the rabbit, 1 leucocyte to 80 erythrocytes, instead of 1 to 1000 as in the normal state. Leucocytosis did not follow the first injection, so that it is very likely to be the consequence of the animal's anaphylactic state. It should be noted, however, that all cachectic animals, whatever may be the cause of their cachexia, show leucocytosis.

The pathological anatomy of animals that have died of acute anaphylaxis scarcely gives any positive information. There is intense congestion with interstitial hæmorrhage in the whole gastro-intestinal tract. The lungs are congested and sometimes also the endocardium and pleura, lesions that can be accounted for by the intense vaso-paralytic dilatation in all the viscera.

Blood in process of absorption is found in the mesenteric lymphatics of those animals which die of chronic anaphylaxis. The intestinal walls are covered by a thick mucous coat, yellowish-red in colour: further, the intestines are quite empty; because dogs with chronic anaphylaxis obstinately refuse food from the moment of the onset of anaphylaxis.

The deep asphyxial inspirations seen in anaphylactised dogs suggest that death is due to true asphyxia. Practically negative results have been obtained in experiments I have carried out in connection with this hypothesis. An anaphylactised animal placed in an atmosphere rich in oxygen (50 per cent. oxygen), immediately after the second injection shows just as intense and as serious symptoms as if it were breathing ordinary air. In another experiment an anaphylactised dog was placed in confined air: the symptoms were rather less serious and vomiting ceased when it breathed freely. But I will draw no conclusions, for I am satisfied that the first experiment was entirely negative and that an excess of oxygen in the inspired air in no way altered the conditions of anaphylaxis.

An important point to be noted is that even in an atmosphere overloaded with oxygen the anaphylactised dog takes deep asphyxial breaths; this would seem to prove that the asphyxia is due to a profound toxic change in the brain and not to deficient hæmatosis.

B.—ANAPHYLAXIS IN THE RABBIT

Arthus gives the following description of anaphylaxis in the rabbit: In a severe case, "at the end of one or two minutes the rabbit shakes its head as if sneezing, shows no signs of apprehension, and lies down. Respirations become polypnœic, from 200 to 250, but not dyspnœic, and are diaphragmatic, shallow, regular, and without abnormal facial movements or thoracic movements; solid fæcal matter is freely evacuated; the animal rolls over on its side, turns its head backwards, moves its paws and then remains motionless, respiration ceasing and the corneal reflex disappearing; it dies after four or five deep heaving respirations. If the thorax be opened immediately, the ventricles will be found to have stopped in systole, the auricles continuing to show occasional and feeble contractions. Generally these symptoms last from two to four minutes."

In a mild case the rabbit shows similar symptoms: "sneezing-like movements, anxiety, distress, polypnœa, fæcal evacuations; it lies on its side and then the phenomena rapidly disappear; it seems practically well. A few days later it becomes cachectic, loses weight; its hair becomes dry, lustreless, shaggy, and falls out in places; it is lifeless, its eyes are dull and its head hangs down. At the end of a few weeks it dies of marasmus."

This last condition may be called anaphylactic cachexia, which differs enormously from acute anaphylaxis. It should be observed that in anaphylactic cachexia lack of food plays an important part; the phenomena are analogous to, if not identical with, those associated with death from inanition.

Besides general anaphylaxis, a true local anaphylaxis has been observed by Arthus in rabbits, which appears after the second injection, more definitely after the third, and terminates in gangrene if the animal is given many injections. Indurated and œdematous infiltrations are produced which are never observed after the first or earlier injections. Local anaphylaxis with similar phenomena, only more marked, have been observed by physicians during sero-therapy treatment.

C.—Anaphylaxis in the Guinea-pig

The following is Otto's accurate description of guinea-pig anaphylaxis after horse serum injections: "A short time, at the most some minutes, after the second injection it begins to be restless, biting its feet and rubbing its nose as if there was something disagreeable and itching irritating it. This is of brief duration; it becomes more and more restless, wandering up and down the cage, lying here and there, until at last, apparently completely exhausted, it lies down unable to rise: if it tries to get up, its strength fails. Most frequently it vomits and passes urine and fæces. Later it is seized with violent convulsions which hurl it from side to side of the cage. Sometimes there are no convulsions, and the exhausted animal remains lying on its side weakened, as if it were paralysed with increased cardiac rhythm and dyspnœic respiratory movements. Frequently the two symptomatic forms of intoxication coincide and the paralytic state follows the convulsive. Friedeman (*Munch. med. Woch.*, 1907) declares there is marked hyperalgesia. When the dose of serum is large, most of the animals die in a few moments of respiratory paralysis. Those which do not die remain for some time with hair bristling, but soon recover, and next day seem practically normal."

The reactions vary remarkably with the technique adopted.

Injections may be made: (1) into the peritoneal cavity; (2) under the skin; (3) into the brain; (4) into the heart; (5) into the jugular vein.

(1) Peritoneal injection is very easy; it has definite advantages: of itself it does not produce symptoms, for the intestines recede before the needle and are never pricked. The procedure is so simple that about thirty guinea-pigs can be inoculated in an hour. But time is of little consequence, and it seems to me that the advantages are counterbalanced by the inconvenience of a variable absorption. Nevertheless, I should observe that Rosenau and Anderson, whose experiments are so admirable and instructive, nearly always adopted peritoneal injections.

(2) Subcutaneous injection is also very simple and in addition very accurate; but the process of absorption varies while it lasts. Frequently it leads to local phenomena which endanger the animal's life.

(3) Intra-cerebral inoculation (Besredka) is a more delicate method. Besides, it is

hardly possible to inject more than 0·5 c.c. of fluid into a guinea-pig of average weight. For testing the effects of very small quantities of fluid it suits admirably. Cerebral injections are not identical with those made subcutaneously into the peritoneal cavity. Comparable experiments alone should be compared and conclusions should not be drawn from the results of different groups. There are numerous instances in which guinea-pigs, intensely anaphylactised by cerebral injections, have presented none of the features of anaphylaxis and have not responded to peritoneal injections.

(4) Inoculation through the heart is not very difficult. Nevertheless, in a large number of cases, symptoms directly due to the operation are observed. One can only be certain of having entered the heart if, after pushing in a very fine needle, blood comes from it in jerks. The blood is usually red, indicating that

either the left heart or the aorta has been punctured. But a guinea-pig's heart is so frail and small that it is impossible to be certain that, as the result of a slight movement on the part of the animal or the operator, the injection has not been delivered elsewhere, the needle transfixing the heart.

(5) Injection into the jugular vein has frequently been tried. The operation is not easy, and requires a certain amount of dexterity, but with practice it can invariably be done successfully. It demands a slight dissection, but in guinea-pigs healing takes place rapidly. I almost think this is the procedure of choice. An incision is made in the neck, near the median line, and after careful dissection of the tissues, which are withdrawn outside the sterno-mastoid, the vein appears, into which the injection is made directly. If done slowly the injection does not flow back through

the prick, and there is no secondary hæmorrhage.

Each worker, however, having accustomed himself to a particular procedure, uses it on all occasions. Rosenau and Anderson, it may be mentioned, have made injections into the eye-ball.

Symptoms, as regards intensity, naturally vary considerably. They can be classified into *highly* fatal anaphylaxis, with death in less than five minutes; *acute*, death occurring within an hour; *chronic*, and death much later; *grave* anaphylaxis with serious symptoms but recovery of the animal; and *mild* anaphylaxis, the symptoms disappearing more or less rapidly: every stage of transition from very grave to very mild anaphylaxis may be observed.

Auer and Lewis prefer the expression *immediate* anaphylaxis. Lewis also (quoted by Otto) has seen in the guinea-pig phenomena of local anaphylaxis, a more or less intense œdema at the site of the second injection. Sometimes it terminates in gangrenous necrosis, which in time leads to the animal's death.

When death has not been sudden, generalised hæmorrhagic congestions in the stomach, intestines, lung, and heart are found at autopsy in dogs for example, which Gay and Southard believe to be the result of capillary degeneration, chiefly in the spleen and glands.

As to the cause of death, the animal dies apparently of asphyxia. But what is the cause of this asphyxia? If it were the result of paralysis artificial respiration ought to keep the animal alive, but it does not. Without being able to bring forward any formal proof of what I state, I believe the asphyxia is hæmatic in origin, that is to say, that the blood being toxic becomes powerless to maintain the life of the nerve-cells, and that therefore there is no question of asphyxia in the true sense of the word.

At all events I am not prepared to accept the opinion recently expressed by Auer and Lewis that it may be due to spasmodic contraction of the muscles of the finer bronchioles.

Firstly, because this cannot be considered the cause of death in dogs. If it were we should be compelled to consider anaphylaxis in the guinea-pig as different from that in the dog, which is inconceivable. Further, as Auer and Lewis themselves have shown, artificial respiration does not prevent death from ensuing or even from occurring very rapidly. It is difficult to imagine a bronchial contraction which cannot be overcome by artificial respiration. Such a type of asphyxia is altogether unknown to physiologists. It must be proved that in spite of artificial respiration *the blood* *is asphyxic, that is to say, that it does not contain oxygen.*

Further, even supposing that the blood in consequence of the constriction of the bronchioles were unable to obtain the smallest quantity of oxygen, two or three minutes would have to elapse before the guinea-pig died. Now, in cases of the most intense anaphylaxis death is even more rapid. I have not seen anaphylaxis supervene less rapidly in dogs placed in oxygen than in those left in normal air. The same experiments should be carried out on guinea-pigs. And before Auer and Lewis's opinion can be accepted, the blood in particular must be analysed, from the point of view of its capacity for oxygen, in curarised and anaphylactised guinea-pigs on which artificial respiration has been carried out.

Again, Auer and Lewis are somewhat contradictory in admitting the existence of cardiac complications and lowering of the arterial blood pressure which reaches 10 millimetres of mercury, phenomena incompatible with the hypothesis of pulmonary asphyxia due to constriction of the bronchioles.

Auer and Lewis base their opinion on an interesting experiment repeated by Biedl and Kraus. It is very simple, and so far has not been controverted. Guinea-pigs which have been given a large dose of atropine do not die of immediate anaphylaxis.

It would appear justifiable to conclude from this that the absence of asphyxia, that is to say, of anaphylaxis, is due to the fact that atropine prevents contraction of the muscle fibres of the bronchioles. But, although the experiment certainly suggests this, it is rash to conclude that atropine has the sole effect of preventing spasmodic contraction of the bronchi, more particularly as artificial respiration does not prevent death, and atropine certainly acts in addition on the central nervous system. Is it possible that excessive artificial respiration should not overcome bronchial spasm? Moreover, this explanation of the guinea-pig's death does not explain the anaphylactic symptoms which supervene in dogs, rabbits, cattle, &c.

There are very wide individual variations in guinea-pigs, as in dogs and rabbits. Animals treated exactly alike do not all respond in the same way. Recently Orsini injected nine guinea-pigs with a second dose of tuberculin on the thirtieth day after the first, with the result that one died in two hours, four in less than eighteen hours, and four survived. Otto records a mortality of 50 per cent. after a second injection of horse serum, although administered under similar conditions in all cases. In Rosenau and Anderson's numerous experiments it is quite clear that although their technique was strictly identical throughout the results were not so.

This is not surprising, for considerable differences are met with even after first injections of toxalbumins. For example, among my own experiments with crepitine, one dog survived a dose of 0·004 c.c. without being sick, while another died in ten hours, having been given only 0·0014 c.c.

Since the first injection affects each individual to a very different degree, the second injection, the effect of which is certainly much more complicated, should also have very different results in different individuals.

It has already been observed that guinea-pigs from Europe, from North America, from Brazil, react differently. In Washington, Rosenau and Anderson state that rapid death by anaphylaxis always follows a second injection of 0·1 c.c. of serum. In France and Germany, on the contrary, according to Besredka and Steinhardt, and Remlinger and Otto, death occurs more rarely. At Rio Janeiro, Vascoucellos, working at the Manguinhos Institute, did not meet with violent anaphylaxis in Brazilian guinea-pigs; it occurred in Argentine guinea-pigs which he had sent to him.

The guinea-pig is the animal of choice for the study of anaphylaxis because it appears to be much more sensitive than the rabbit; and although experiments on dogs yield more information, it is absolutely impossible to carry out as many as on guinea-pigs.

To ascertain the degree of anaphylaxis better, Pfeiffer made observations on the guinea-pig's temperature. This investigation has been carried further by different workers, notably Sadanori Mita, who gives a complete bibliography on the subject.

Apparently the intensity of anaphylaxis can be estimated by the temperature, although the guinea-pig's temperature, as all physiologists know, is difficult to take exactly and is modified by very slight influences.

The tenth of a centigrade degree is taken as a unit, and the minimum temperature is recorded; note is also made of the time at which this minimum was observed. It can be proved in this way that there is a definite relationship between the anaphylactic symptoms and abnormally low temperature, cases in which death supervenes being excluded; for death sometimes occurs so soon that there is not time for the temperature to fall.

Symptoms appear when the fall in temperature amounts to 3·5° or more. It has been noted that the greater the fall in the temperature, the longer it takes for the animal to return to its normal state.

Pfeiffer has suggested a formula by which the intensity of anaphylaxis may be estimated by hypothermy. Let Θ be the time during which the temperature is reduced, and A the full fall in temperature; anaphylaxis will have its formulæ $\frac{\Theta A}{2}$, the time being measured in minutes and the fall in tenths of a degree below 38°.

In applying this formula, it will be seen that in animals which are to recover from anaphylaxis, ΘA ought to be below 30·000.

S. Mita gives several interesting examples of this measurement of the degree of anaphylaxis. I will only quote the following: "Twenty-one days previous ten guinea-pigs received 0·01 c.c. ox serum. They were then injected in pairs with second doses of the same serum amounting to 0·5 c.c., 1 c.c., 1·5 c.c., 2 c.c., 2·5 c.c.: the formula gave for each 600, 4050, 4725, 9195. By no other means could such accurate results have been obtained."

I have observed very low temperature in dogs too, in one instance the extraordinarily low degree of 19·3°. But I have not undertaken any methodical researches in connection with this question, which is rendered still more complicated in the case of guinea-pigs by their individual differences.

D.—OTHER ANIMALS

It ought to be possible to observe a phenomenon so striking as anaphylaxis in all animals, nevertheless Doerr has not seen it in white mice, in spite of numerous experiments, nor has Frey, who is quoted by Doerr. It has been observed in horses (Kraus); in goats, which are extremely sensitive (Kraus and Stenitzer, Kraus and Doerr); and in rats (Arthus).

It should be stated that anaphylaxis in rats has been called in question. B. Galli-Valerio has not been able to induce it in *Mus ratus* and *Mus decumanus*, though guinea - pigs experimented on under similar conditions presented very intense anaphylactic phenomena. Galli-Valerio thus confirms the experiments of Frey, Doerr, Trommsdorff, Uhlenhuth, and Weidanz, who also have not been able to anaphylactise rats.

Alexandrescu and Ciuca (1910) studied the phenomena of anaphylaxis in cattle after anti-anthrax sero-vaccination. Out of a total of 70,000 animals twice vaccinated, they observed anaphylactic symptoms in 10 per cent. ; in a single instance death ensued.

They distinguish several degrees :—

1. The fulminating form : with intense dyspnœa, tremendous œdema of the udder, cyanosis of the mucous membranes, abundant, salivation, collapse of the animal with generalised convulsions.

2. The very grave form : with dyspnœa, pulmonary œdema, vertigo, lassitude lasting about three-quarters of an hour.

3. The grave form: with intense prurigo of the muzzle and anus; impulsive forward movements, urticaria; the whole lasting about half an hour.

4. The slight form: with œdema of the muzzle, anus, and vulva, cyanosis of the udder, urticaria, absence of rumination.

The same authors have also observed anaphylaxis in the horse, marked by extreme excitement, œdema, and urticaria.

Friedberger and Hartoch have produced anaphylaxis in pigeons and describe it thus: "Immediately after the injection the bird takes deep asphyxial breaths. Its beak opens and it throws out foam and mucus. Its feet tremble; it is unable to fly; it falls as if exhausted; it loses its equilibrium; its respiration becomes polypnœic, and then at the end of ten to twenty minutes the serious symptoms relax, and by the end of an hour it has returned to its normal state. Death rarely follows the first injection, but almost always the second inciting injection."

Arthus has also seen anaphylaxis in pigeons and ducks. As to cold-blooded animals, Friedberger and Mito state that they can be anaphylactised. (*Zeitschrift für Immunitasforschung und experimentelle Therapie*, 1910, viii. p. 245.)

E.—ANAPHYLAXIS IN MAN

The symptoms of anaphylaxis in man are chiefly seen in those, more particularly children, who have been given injections of anti-diphtheritic serum on separate occasions. Arthus was the first to study the anaphylactic action of serum, with what success is well known. In 1903, on the suggestion of Calmette, who had himself experienced the very painful and dangerous effect of a second injection of serum, he studied the effect of repeated injections, and immediately after I had described in 1902 the effects of anaphylaxis he verified them.

Since the earliest use of sero-therapeutic injections definite phenomena have been observed to follow them, and naturally, as I was the first to use them, I was the first to describe them (*Bull. de la Soc. de Biologie*, 1891, 17th January): they included erythema, pruritus, more or less generalised urticaria, with slight fever and malaise. Later other observers saw and described them. But until Pirquet and Schick in 1903 drew attention to it no relation had been observed between these sero-therapeutic manifestations and the fact that they were not primary. It had not been recognised that they only occurred after second or third injections; that is to say, that they were anaphylactic phenomena.

Pirquet and Schick called these symptoms serum disease, and they have given a detailed description of it.

It must be noted that, in certain instances, a first injection of horse serum is quite capable of inducing such symptoms as urticaria, arthritis, nausea, vomiting, œdema, pruritus.

It has even been stated that normal horse serum, the serum of horses not immunised with diphtheritic toxin, can produce symptoms in predisposed individuals.

It may therefore be asked if there is not such a condition as spontaneous, natural, or idiosyncratic anaphylaxis. But the word idiosyncrasy explains nothing; it would be better to suppose that there was such a condition as special anaphylaxis induced by diet. This would practically account for the fact that symptoms invariably follow the first injection of horse serum into those who, for therapeutic purposes, take a raw horse-flesh diet. (Unpublished work, de Rist and Ch. Richet, junior). Certainly some individuals who have never eaten raw horse-flesh are sensitive to a first injection of horse serum; but the more or less rigorously specific limits of the anaphylactising antigen have not yet been so defined as to enable us to say that there were not in their diet substances capable of developing a special anaphylactic state against horse serum. Therefore, this statement, which has been formally made, appears to us of very great importance in proving that an undoubted anaphylactic state to horse serum can be induced by horse-flesh diet.

Reaction however to a first injection is exceptional; on the contrary, reaction to a second injection is constant.

Pirquet and Schick distinguished an *immediate* and a *delayed* reaction. Immediate reaction after the second injection sometimes only occurs a quarter of an hour after the injection with urticaria, vomiting, pruritus, coma. In some very exceptional instances there is an immediate reaction in individuals who have not received a first injection. The delayed reaction observed in predisposed individuals, who are exceptional from the eighth to the twelfth day, usually the tenth, appears sooner in reinjected individuals, that is to say, about the fifth or sixth day. The reaction is then always hastened, although never immediate. The following table, dealing with ninety-one cases of anaphylaxis, is given by Pirquet and Schick :

Interval between the First and Second Injection.	Reaction only Immediate.	Reaction Delayed.	Reaction both Immediate and Delayed.
From 10 days to 1 month	21 (87%)	0	3 (13%)
From 1 month to 6 months	21 (63%)	5 (15%)	7 (22%)
Over 6 months . .	2 (6%)	30 (88%)	2 (6%)

Pirquet and Schick have called this phenomenon of reaction of an organism to a foreign substance *allergy*, but it seems to me unnecessary to introduce this word along with anaphylaxis.

There is a local as well as a general anaphylaxis, as has been seen by Arthus in rabbits. And it certainly is not one of the minor difficulties of the question to find, not only the blood and viscera, but all the tissues, skin, and lymphatic glands saturated with the poison.

Although the symptoms may be intense and sometimes even alarming, most frequently they end by recovery. Nevertheless there have been fatal cases. A well-known physician who had given himself an injection of antiplague serum, repeated it a year later, and died in a few hours of fainting fits, coma, and asphyxia. Doerr states that there are nearly twenty published fatal cases, but he added that in some instances death was probably as much due to the diphtheria as to the serum. Pinara has informed me of a case in which a second injection of Marmorek's antistreptococcic serum was followed by serious symptoms. Doerr also quotes two very serious cases, one Otto's, the other Flexner's, neither of which, however, ended fatally.

Since in all these cases of anaphylaxis in man the injection has never been given intravenously, and nevertheless the symptoms have been very serious, and since a large number of experiments on animals have proved that intravenous injections induce more rapid and more intense symptoms than subcutaneous injections, it can be concluded definitely :

1. That man is extremely sensitive to the anaphylactic reaction.

2. That intravenous second injections invariably constitute an actual danger.

CHAPTER VI

ON ANAPHYLACTISING SUBSTANCES IN GENERAL

It will be convenient, in the first place, to exclude those substances, toxic or non-toxic, which do not induce the anaphylactic state after a preliminary intravenous injection. I have already mentioned the experiment performed by Aducco, who, in 1894, observed that dogs were more sensitive to the action of cocaine if they had received a previous dose. But it is impossible to say that it was not a phenomenon of accumulation at the end of three or four days, his experiment merely showing a slightly more rapid rise of temperature, the result of doses administered very soon after each other.

I attempted to repeat Aducco's experiment with cocaine on rabbits, and I was unable to demonstrate true anaphylaxis either in them or in guinea-pigs; at least the reactions were so feeble that no conclusions could be drawn. Apomorphine gave somewhat more significant results. While studying its emeticising dose on the dog by intraperitoneal injection, it seemed to me that sensitivity was slightly increased. But, as individual sensibility is in some dogs more than double that in others, 0·0005 to 0·00019 gramme of apomorphine hydrochlorate injected into the peritoneal cavity being required to produce vomiting, it would be rash to infer an anaphylactic reaction. Nor has Doerr observed anaphylaxis to follow the injection of strychnine. Rosenau and Anderson have tried tyrosin and leucin without effect.

Possibly some day it will be found

that a mild anaphylaxis follows the injection of crystalloids; but up to the present everything seems to prove that colloids alone are able to induce it; just as colloids alone are capable of producing the reactions of immunity. There are some crystallised albuminoids, like edestine, which Rosenau and Anderson used in a very pure form without obtaining anaphylaxis in guinea-pigs.

Crystalloids do not induce anaphylaxis, but colloids, almost without exception, are capable of inducing it. I have seen extracts of the bodies of actinaria (*Anemonia sulcata*, *Anthea cereus*), of suberites (*Suberites domuncula*), and of mussels (*Mytilus edulis*) induce it. Arthus has seen it follow injections of horse serum; and innumerable investigators have shown that it follows the injection of heterogeneous sera such as ox serum, eel serum, goat serum without exception.

The term heterogeneous serum means serum of an animal of different species. But there are not only specific differences, there are also individual differences, so that the serum of one individual is to a certain extent heterogeneous to another though their species be the same.

I have endeavoured to avoid this question. It is interesting because it introduces into science *individual physiology* which has not yet been touched upon, or only very slightly, and I venture to assert that the results so far have been practically nil.

In this connection I injected a certain quantity of blood into several dogs by direct transfusion, and one month later reinjected each with blood from the same animal as before. The amount of blood which can be injected by direct transfusion without causing death is about 10 per cent. to 12 per cent. of the body weight of the recipient. Now if one month later transfusion is repeated, 5, 6, 7, 8, or even 9 per cent. can be injected without producing symptoms and without there being any symptom of anaphylaxis.

Negative experiments do not permit definite conclusions, but it seems clear that the injection of a specifically homogeneous blood does not induce anaphylaxis.

Innumerable experiments have been performed with heterogeneous sera. Others have been made with the most diverse albuminoid substances — for example, egg albumen (Majendie, 1839; Vaughan and Wheeler); milk (Arthus, Besredka); all kinds of organic extracts as red blood corpuscles, spermatozoa, the vegetable albuminous extract from kidney beans (Raubitschek) and from *Hura crepitans* (Ch. Richet); extracts from rice and wheat (Karasawa); linseed oil, castor oil, cacao butter (Uhlenhuth and Haendel); the albumotoxins produced by micro-organisms (Kraus and Doerr); yeast (Rosenau and Anderson); and dead micro-organisms. All the substances in this group are albuminoids. Therefore it is the albuminous substances which do not lead to anaphylaxis that should be sought, rather than those which do. For if they do exist, which is doubtful, they must be very few in number.

Abelous and Bardier isolated from human urine a hypotensive substance, insoluble in alcohol, soluble in water, precipitated by ammonium sulphate and non-dialysable, which is manifestly anaphylactising in the dog and rabbit.

Pozerski has proved that papain induces both local and general anaphylaxis.

Dungern and Hirschfeld have seen the injection of testicular fluid into rabbits' ears induce a definite reaction after a first injection, and an extremely marked reaction after the second.

Rosenau and Anderson have observed that an injection of placental extract is anaphylactising. Gozony and Wiesinger discovered an interesting fact on repeating this experiment. Serum from two eclamptic women was injected into guinea-pigs, and, forty-eight hours afterwards, these were given an injection of normal amniotic fluid, which led to fatal anaphylactic phenomena, although amniotic fluid has no action on normal guinea-pigs. It may be inferred, though the experiment ought certainly to be repeated, that the serum of eclamptic women contains substances which anaphylactise against the albuminoids of amniotic fluid. This may have some pathogenic relation to puerperal eclampsia.

I thought that emetine, a crystallisable substance which can be prepared in very great purity, might confer the anaphylactic state. And, as a matter of fact, in doses of about 0·004 c.c. on intravenous injection into dogs it excites vomiting, diarrhœa, and death at the end of two or three days, with intestinal hæmorrhage and an intense congestion of the whole of the alimentary mucosa. However, it is practically impossible to be certain of the presence of anaphylaxis, although *in certain instances* somewhat similar phenomena, intense pruritus, &c., appear at the time of the second injection, when made from thirty to fifty days after the first.

Although definitely crystallisable substances do not produce anaphylaxis, certain drugs like quinine, antipyrin, and iodoform are apparently exceptions, and in some predisposed people they inevitably lead to urticaria and anaphylactic sickness. Bruck carried out a curious experiment in this connection. The blood of a patient, known to be sensitive to iodoform, was injected into guinea-pigs. When they were injected with iodoform in doses which were harmless to normal guinea-pigs, anaphylactic symptoms developed. This experiment was repeated by Klausner with similar results. Bruck thought there was question here of anaphylaxis, indirect in some way, produced by proteid substances derived from the action of iodine on the proteins of the animal. Here again, as in many of the problems we are touching, probably fruitful research work might be undertaken.

H. G. Wells performed interesting experiments with a pure crystallisable albuminous extract from eggs. He proved that in order to sensitise a guinea-pig the infinitely small quantity of 0·000,000,05 gramme is required, and for the reacting dose the very small quantity of 0·000,05 gramme suffices. This albumen loses all its toxicity if heated at 100° for forty-five minutes, but it still remains capable of sensitising. Wells has also studied the influence of tryptic digestion on this albumen, and he discovered that at the end of a very long time the sensitising power was diminished. But the diminution is slight, particularly if the duration of the experiment is considered. After fifty-nine days of digestion crystallisable albumen was still capable of sensitising in a doze of 0·1 gramme.

Doerr, judiciously summarising, as is his custom, these experiments on the chemical action of albuminoid substances, so far as they are anaphylactogenic, concludes thus :

1. The anaphylactising substances are albumins and globulins from serum; albumens from white of egg.

2. The anaphylactising power is rapidly affected and partly destroyed by chemical action. The resultant substances, which

are active, may behave either as sensitising agents or as toxins, according to their quantity.

3. No chemically formed substance can be anaphylactogenic. Abderhalden and Weichardt only obtained negative results by using acid amides.

Peptones lie between colloids and crystalloids. But it is difficult to experiment with them, for commercial peptones, like Witte's peptone, are very complex products. Arthus obtained visible though slight anaphylaxis in the rabbit with Witte's peptone. Rosenau and Anderson only obtained very weak anaphylaxis. Biedl and Kraus thought that anaphylaxis could be produced by peptone, and they even inclined to the belief—though they have not formally expressed it—that all the phenomena of anaphylaxis are due solely to peptones. This opinion seems impossible to accept, and is one upon which there are no grounds to insist, inasmuch as the amount of peptone contained in serum is infinitesimal; consequently it would have to be admitted that the dose of peptone likely to produce anaphylaxis would be in some instance 0·000,000,001 gramme, which is very unlikely.

Gelatine, like peptone, is practically ineffectual; Arthus performed two experiments in this connection, but neither is convincing.

Pick and Yamanouchi attempted to alter albuminoids by chemical action and observed that digestion of serum by pepsin hydrochloride did not prevent anaphylaxis from ensuing. Serum, after tryptic digestion in an alkaline medium, can occasionally produce anaphylactic phenomena, but most frequently they do not appear. The nitric acid precipitate of serum-albumin (xanthoprotein), like its iodide, does not prevent anaphylaxis, though it becomes somewhat irregular.

This fact was observed also by Rosenau and Anderson.

Hartoch and Ssirenskij have gone further. They observed that by bringing serum into contact with pancreatic trypsin products were obtained which, even on first injection, led to toxic symptoms more or less analogous to those of anaphylaxis. They concluded that the anaphylactic state is due not to albumin itself, but to certain of its cleavage products, probably more or less analogous to peptones. This effect of various chemical agents on the anaphylactising antigen has been much studied, not only because its theoretical interest is very great, but especially because from a practical point of view it would be of enormous importance to destroy, or, at least, to diminish the anaphylactising effects of serum.

Rosenau and Anderson have greatly added to the number of these experiments with different chemical agents, in particular with permanganate of soda, which I have also tried in 1 per cent. dose without result. In their experiments, and in those of other workers, all the evidence goes to show that the anaphylactising antigen is extremely resistant to chemical action. As long as the albuminoid molecule is not completely destroyed, even when it is extensively broken up by tryptic digestion, it remains capable of producing anaphylaxis.

It will be enough for me now to mention some of the various substances which according to Besredka have been employed: butyric acid, calcium citrate, chloroform, invertin, myrosin, emulsin, morphine, strychnine, peroxide of hydrogen, the salts of magnesium and ammonia, ox bile, formol, &c. The anaphylactising antigen passes through porcelain filters, diffuses through collodium bags, is not altered by Röntgen rays, is not absorbed by cerebral cells, nor affected by coagulation. A temperature of 100° to 105° does not destroy its anaphylactising effect. These, however, are merely rough statements, and analysis of their very numerous details is required.

Now it is essential that various terms should be defined precisely in order to try and bring some clearness to an obscure subject.

There are in fact two distinct groups of phenomena which must be differentiated. Firstly, there is *preparation* for the anaphylactic state—that is to say, the injection of anaphylactising substances, which we will call for simplicity *preparatory* substances; and, in the second place, there is the *exciting* of anaphylaxis by the second injection, with the production of the leading symptoms of anaphylaxis itself; we shall call these *exciting* substances.

We have then to consider what are the preparatory or anaphylactising substances and what are the exciting substances producing anaphylactic shock. In most instances this preparatory substance is the same as the exciting substance, and this would always be so if specificity were absolute. We shall see presently that remarkably definite as this specificity is, that is to say, the identity between the preparing and exciting substance, nevertheless it cannot be maintained that it is absolutely perfect.

We shall first study the effect of heat on albumins so far as they are preparatory substances.

Besredka, in his interesting studies, calls those substances which lead to the anaphylactic state *sensibilisines.* But as they include all albuminoid substances, it seems to me better to give them a more general name, which will imply no chemical analogy in their structure, and to call them *preparatory* substances.

From the beginning one fact is evident if investigation is made with toxalbumins. It is that heat enormously diminishes their toxic action even without coagulation. Now, in spite of this elimination of the toxic property of the toxin, there remains in it nevertheless an efficient anaphylactising substance. For example, unheated crepitine, which is toxic in doses of 0·001 gramme, is toxic in doses of 0·03 gramme after heating, and similarly with congestine. Moreover, these heated toxins are efficient not only at the time of the first or anaphylactising injection, but also at the time of the second or exciting injection.

It appeared to me too that, in order to develop an intense anaphylactic state, it would be advantageous to use heated toxins; for they could then be injected in stronger doses.

It is practically the same with horse or ox serum, the toxicity of which can be remarkably diminished by heating to 60° (Rosenau and Anderson, Besredka, Doerr, &c.).

Occasionally the effect of heat on toxins is complex. For if, instead of heating them at from 50° to 60°, they are heated in some diluting and alkaline solution between 45° and 50° for some hours, the toxicity is increased to a considerable extent, from one to three or four times. I do not say that this is always true; but I have definitely proved it in connection with the different varieties of crepito-congestine and actino-congestine. So that above 60° the activity of toxins is diminished; from 40° to 50° it is increased. In no case is the anaphylactising power diminished. The actual temperature at which the latter is destroyed has not been ascertained with certainty, but it would seem that it varies in different substances. I have noticed that the anaphylactising effect of actino-congestine is diminished after it has been heated at 103° for three minutes. This is not generally true; for the *preparatory* power of crepitine is not destroyed by heating at 103° for three minutes, as is shown in the opposite table in which the *preparatory* dose was heated crepitine and the *exciting* dose unheated crepitine.

It should be noted that in the case of dog No. 6 anaphylaxis was only manifest by intense itching and an unusually severe pruritus lasting nearly twenty minutes.

Rosenau and Anderson in 1908 noticed that anaphylactic effects disappeared almost, though not quite, completely when a 1 in 3 solution of horse serum was heated for an hour at 100°; of seven guinea-pigs thus treated, three showed doubtful anaphylactic symptoms.

What makes it difficult to draw con-

Dog.	No. of Days between the two injections.	Preparatory Dose (in milligrammes per kilogramme).	Exciting Dose (in milligrammes per kilogramme).	Anaphylaxis.	No.
No. 1	50	11·4	4·0	Severe	1
No. 2	37	23·0	1·0	None	2
No. 3	34	3·3	4·0	Severe	3
No. 4	33	3·5	1·8	Pretty severe	4
No. 5	31	14·0	6·0	Weak	5
No. 6	30	14·8	1·0	Pretty severe	6
No. 7	29	16·8	0·28	Very severe	7
No. 8	28	41·0	4·7	Weak	8

clusions is the fact, as Rosenau and Anderson have noted, that extremely minute doses of serum can anaphylactise, so that anaphylaxis is observable even if only a hundredth part of the serum has not been decomposed by heat.

They therefore consider—and in our opinion with good reason—that the effect of heat on serum is due to a great extent to coagulation ; for serum, egg albumen, and desiccated milk can be heated at 170° without losing their *preparatory* properties. Desiccated milk heated at 170° for ten minutes is just as anaphylactising as fresh milk. The same is true of dried horse serum, which retains its *preparatory* power though heated for two hours at 130° or for ten minutes at 170°.

This ingenious experiment is in accordance with all we know concerning the resistance of dried albumins to heat.

But these are special conditions, and when a thermostable substance is spoken of, thermostable in aqueous solution is understood. Many things make the experiment difficult to explain fully; for, to avoid coagulation, the serum (or toxin) must be diluted; and then again, in connection with the effect of heat, how does its duration compare with its intensity? Is a temperature of 120° lasting three minutes comparable to a temperature of 100° lasting thirty minutes, or one of 90° lasting an hour?

We must be contented with this general though rather vague statement which nevertheless is true as far as it goes, that *toxicity is much diminished and the anaphylactising power considerably diminished* by heat.

Like Doerr and Besredka we may then suppose that the anaphylactising substance whatever it may be is, when in solution, slowly destroyed by heat; it is therefore to some extent thermolabile in aqueous solution.

Similar difficulties meet us on approaching the study of the *exciting* substance.

In some cases the toxin, though heated at 103° for three minutes, retains its *exciting* power, as the following experiment shows: Three dogs received on the same day the following doses of congestine which had been heated at 103° for three minutes, the first 0·025 gramme per kilogramme; the second 0·025 gramme per kilogramme; the third 0·08 gramme per kilogramme. A dose of 0·055 gramme of unheated congestine was toxic. The last, a young dog, showed no symptoms. The first, which received 0·05 gramme of heated congestine sixty-six days previously, was very slightly ill; the second, which received 0·05 gramme of unheated congestine sixty-six days previously, died in two hours with severe hæmorrhages into its alimentary canal.

But, on the other hand, the *exciting* properties of a serum are greatly diminished by heating (Rosenau and Anderson; Besredka).

Besredka heated three separate quantities of serum for twenty minutes at 76°, 89°, and 95°, and he injected 0·25 c.c. of each sample into the brain of two sensitised guinea-pigs: 0·25 c.c. of this same serum, unheated, killed sensitised guinea-pigs. Now, of the two which received the serum heated at 76° one was pretty ill but recovered; the other practically showed no reaction. The other four, which were given serum heated at 39° and 95°, showed no, or practically no, reaction.

Similarly Rosenau and Anderson demonstrated that by heating serum at 100° for an hour they made it lose all its *exciting* power. Of six guinea-pigs reinjected with such a heated serum, none were ill.

Besredka, therefore, is of opinion, since some *preparatory* substances are relatively thermostable, and some exciting substances are relatively thermolabile, that there are two different substances in the serum ; one *preparatory* (sensibilisin), which is not destroyed by heat; the other *exciting* (antisensibilisin), which is destroyed by heat. Kraus and Volk have carried out experiments which fully confirm Besredka's opinion. They are of opinion that there are two groups of substances in horse serum : one *preparatory*, the members of which are thermostable, and the other *exciting*, the members of which are thermolabile and probably allied to albuminoids if they are not themselves actually albuminoids, and disappear when the albuminoid coagulates. Consequently, when an animal has been sensitised by heated serum, anaphylaxis may be excited by unheated serum. In passively anaphylactised animals, on the other hand, anaphylaxis is only excited by unheated serum. But in reality this severance by heat of the *preparatory* and the *exciting* power is uncertain. Even Doerr and Russ, as a result of their researches, in a sense take up an attitude directly opposed to Besredka's and to Kraus and Volk's opinions and declare that the preparatory and exciting substances are identical; for they behave similarly when heated, that is to say, that sera heated at 80° lose both preparatory and exciting properties at once. In any case, when discussing the effect of heat on the preparatory and exciting properties of antigens, we must be careful not to generalise, for various organic fluids behave differently. Further, the degree of dilution plays an important part. Milk can be heated at 130° without losing any of its preparatory or exciting power. May not this be due to the fact that milk heated to 130° does not coagulate?

The more this question is considered, the more difficult it is to answer, and the more unwise it is to frame any general theory on the effect of heat.

In addition to all these attempts to separate the *preparatory* and exciting substances of serum by heat, we must mention the important work of Gay and Adler, and Gay and Southard, who endeavoured to carry out the separation by chemical means.

They used ammonium sulphate, which precipitates albumins. If to serum is added a third of its volume of a saturated solution of ammonium sulphate, a precipitate is obtained which has lost its *exciting* power but retained its *preparatory* power. Gay and Adler termed it *euglobulin*, though previously they named it *anaphylactin*. It is typical of the group of preparatory substances, inasmuch as it does not contain the *exciting* agent. It should be remarked that it induces the anaphylactic state more rapidly than normal serum, in five days instead of ten.

Doerr and Raubitschek added carbon dioxide to diluted horse serum. The precipitate (globulin), redissolved and injected into guinea-pigs, is anaphylactising, but anaphylaxis only appears at the end of thirty-three days, whilst other guinea-pigs which were given the non-precipitated portion of the serum were already anaphylactic in twenty-two days. Briefly the experiment is less convincing than Gay and Adler's, for no proof is forthcoming of the *exciting* power of carbonic globulin.

Vaughan and Wheeler endeavoured to isolate the toxic substance in white of egg with alcohol. But in their work they added a 2 per cent. solution of soda, and at a temperature of 78° this toxic substance, soluble in alcohol, is *preparatory;* but it does not seem to be *exciting.* In any case, even the *preparatory* attributes of the alcoholic extract are not comparable to those of unaltered egg albumen.

I believe I have succeeded in definitely separating the *exciting* and *preparatory* powers of antigens, notably in the case of actino-congestine.

If crude congestine, precipitated from the aqueous extract of actinaria, be treated with four times its volume of 95 per cent. alcohol, and be several times redissolved and precipitated by different strengths of alcohol, two bodies which are very different from one another may be obtained by dividing the precipitations: one is greyish, mucoid, insoluble in fluids containing 35 per cent. alcohol and slightly soluble in water; the other is yellow, dichroic, very soluble in water and in fluids containing 50 per cent. alcohol. We will call them simply *black* congestine insoluble in 33 per cent. alcohol, and yellow congestine soluble in 50 per cent. alcohol. Now the toxicity of both these substances, when dried and freed from impurities, is almost identical. The limit of the toxicity of black congestine is about 0·045 gramme; and of yellow congestine, 0·055 gramme. After many different experiments, too numerous to be mentioned here, I found that black congestine is in no sense *exciting* although slightly more toxic than yellow, but that it is a better *preparatory* agent than yellow. The following is an experiment proving this:

Each of four dogs was given 0·04 gramme per kilo. of congestine. The first and second received black congestine, the third and fourth yellow congestine. Thirty-five days later, a second injection of 0·01 gramme of black congestine was given to the first and to the third without effect. On the other hand, on injecting only 0·002 gramme of yellow congestine into the second and 0·0029 gramme into the fourth, I induced in both well-marked symptoms of anaphylaxis, specially in the second, which died in three hours without recovering from the initial shock. The fourth animal presented very serious symptoms, apparently recovered, but died during the night.

This experiment permits us to draw an important and definite conclusion: that specificity is not absolute, *that the preparatory and exciting substances are not the same;* for black congestine is not *exciting* and is more *preparatory* than yellow. When speaking of the specificity of anaphylactic reactions we are not concerned with pure homogeneous products, but rather with mixed substances. Obviously when using horse serum we are using a very complex substance. Congestines obtained from actinaria, from *Hura crepitans*, although more homogeneous, are nevertheless mixtures of very similar substances which it will be found difficult to separate. All these points suggest that the sensitising or preparatory and the exciting attributes are properties of two groups of albuminoids or of substances allied to the albuminoids which are not identical. Difficulty lies in the selection of means to dissociate them. Bio-chemistry will have the final word in this matter, but it is a special branch of bio-chemistry.

So that if we speak of the specificity of anaphylactic reactions it is because the *preparatory* substance always coexists with the *exciting* substance in the organic fluids we use. From this point of view the experiment made with the congestine of actinaria is very instructive. Had I worked with crude congestine I should have inferred that specificity was rigorous; but by isolating two different, though analogous, substances from complex congestine it can be proved that specificity is not absolute, although congestine, which is most active as an anaphylactiser, has no exciting action.

If it is true, as Besredka's experiments with heat would lead us to suppose, that known organic fluids include both substances, and that they are always in association with one another, we might be tempted to believe in specificity, inasmuch as the same liquid is employed. Ox serum contains a special preparatory substance and an exciting substance allied with it; horse serum contains a special preparatory substance and along with it a special exciting substance. Moreover, ox serum only prepares against ox serum and not against horse serum; cow's milk only prepares against cow's milk and not against mare's milk. This and no more may be said; it may not be concluded that the *preparatory* substance is identical with the *exciting* substance.

In many instances there is no manifest absolute specificity of the anaphylactic reaction. Specificity does not manifest itself on account of the type of a particular tissue. Ranzi injected guinea-pigs and rabbits subcutaneously with extracts of the organs of horses, sheep, man, and extracts of malignant tumours, and he observed that the animals were anaphylactised to all the organs and the serum of animals of the same species to this extent, that the anaphylaxis is limited to the animal species, and not merely to the particular substance injected, whether from glands, muscles, liver, or blood.

There is one remarkable exception to this, namely, crystallin. P. Andrejew observed that extracts of crystallin, whatever be the animal species from which they are obtained, anaphylactise an animal of a different species, but do not anaphylactise against extracts of organs, so that in this instance it is specificity of an organ and not specificity of the animal type which is in action.

Even authorities like Rosenau and Anderson, who are firm believers in the specificity of anaphylaxis, acknowledge that it is only relative; for example, mare's milk and ass's milk anaphylactise for both.

Although crepitine and actino-congestine are absolutely different from each other in their origin, their toxic dose, and their effects, nevertheless I have seen them induce some degree of anaphylaxis to each other. I think it can be definitely demonstrated if waited for a very long time. Two dogs, which were given crepitine eight months previously, and were in a perfect state of health, showed very intense anaphylactic symptoms and soon died in convulsions, which is rare in dogs, after receiving a dose of actino-congestine. I should add that some other animals previously treated with crepitine, as these were, showed nothing analogous. On the other hand, I have seen two dogs, which a long time previously were injected with congestine, present symptoms of intense anaphylaxis after the injection of crepitine, showing that in the case of these two very different poisons, crepitine and congestine, the anaphylactic phenomena are interchangeable.

Gay and Southard have also insisted on the relative specificity of anaphylaxis. They gave a group of nine guinea-pigs a *preparatory* injection of egg albumen. Three of these received an *exciting* injection of egg albumen: two died. Three others were given horse serum: one died and two were ill. Three were given milk: two of these were ill.

Again of six guinea-pigs, which were given milk in *preparatory* injection, two were given an *exciting* injection of horse serum and became obviously ill; two others were given egg albumen and showed very mild anaphylactic symptoms. Moreover Gay and Southard conclude, on the result of these experiments and those with euglobulin which I mentioned previously, that the sensitising or *preparatory* substance, *anaphylactin*, need not be identical with the substance which excites symptoms and intoxicates on second injection.

It has been seen that our experiments with black and yellow congestine fully confirm this conclusion.

Now to say that the preparatory and exciting substances are not identical is really to deny the specificity of anaphylaxis. But from a practical point of view specificity is absolute; for it is proved, as we have shown, that in the complex fluids (extracts of organs, animal and vegetable albumins, sera, microbial culture fluids) employed two substances, *preparatory* and *exciting*, always coexist, if some degree of separation has not been brought about previously by chemical means. Suppose the *preparatory* substance be called A, the *exciting* substance B; since A + B are always present in organic fluids, we speak of specificity, for we have nothing to do with the mixing of A and B.

With this reservation — which is a detail — the anaphylactic phenomena are most often rigorously specific, so much so that it is possible to distinguish anaphylaxis brought about by ox, sheep, dog, or human blood; by cow's, mare's, or human milk, &c., with such a degree of accuracy that this process of diagnosis might be made use of in forensic medicine.

CHAPTER VII

ON ANAPHYLACTISING SUBSTANCES IN PARTICULAR

1. *Sera.*—The researches of Arthus, Theobald Smith, Otto, Rosenau and Anderson, and most authors, are based on anaphylaxis induced by sera, so that a large proportion of the facts previously mentioned refer to serum anaphylaxis.

Rosenau and Anderson studied the dose of the *preparatory* injection and discovered this extraordinary fact that guinea-pigs can be anaphylactised with minute quantities of serum, even with as little as 0·000,001 c.c. To realise the smallness of this quantity it will be sufficient to consider that the amount of active substance contained in the serum is at most only a hundredth part, possibly a thousandth, perhaps still less, so that there may actually be in question a dose as small as 0·000,000,000,1 gramme.[1]

However, in general, stronger doses are necessary, about 0·01 gramme under the skin or 0·001 gramme into the brain, to obtain constant anaphylaxis in all cases.

Following stronger doses anaphylaxis takes a longer time to appear. *It seems that anaphylaxis can only develop when all the preparatory substance has disappeared.* This fact is important; it explains the remarkable observations made by Besredka while studying anti-anaphylaxis, which we will discuss later.

Usually the *exciting* dose should be stronger than the *preparatory* dose. This is the reverse of what occurs in anaphylaxis induced by toxins.

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[1] I showed that extremely weak doses of a metallic salt may affect lactic fermentation; for example, vanadium chloride in the minute dose of 0·000,000,000,1 gramme per litre (Physiology Lab. Rep., 1909, vi. p. 353).

The specificity of sera is remarkable. The *exciting* substance ought to be the same as the *preparatory* substance. Previously we saw that this is only apparent, since in reality they are different. But it is no less true that a guinea-pig, into which horse serum has been injected, is not sensitive to ox, rabbit, dog, or eel serum, and inversely. This statement, which is incontestable, is nevertheless only true within certain limits. Bruynoghe in some instances observed that guinea-pigs which had been given a *preparatory* injection of ox serum reacted intensely after massive injections of horse serum, and similarly of sheep serum.

Like Gay and Southard, Bruynoghe tried to isolate the anaphylactising substance or substances of the serum. His conclusions are important. They are as follows:

(1) The dialysable substances of serum are not anaphylactising.

(2) The filtrate obtained after total precipitation of the albuminous substances of serum is not anaphylactising.

(3) The various albuminoids of serum, isolated by Hofmeister's method, increase sensitivity—and all to the same degree of intensity—to a second massive injection of serum. This fact had already been observed by Waele.

(4) Euglobulins do not induce more marked supersensitivity than pseudoglobulins or serins, which is contrary to Gay's opinion.

2. *Milk.*—Firstly Arthus' experiments, Rosenau and Anderson's, then Besredka's definitely proved that anaphylaxis can be brought about by milk.

Rosenau and Anderson have shown the specificity of this reaction. Guinea-pigs sensitised with human milk only react to human milk and not to cow or goat milk, and inversely. The specificity is very definite but not absolute, and is still less so when concerned with closely allied species of animals; cow milk slightly anaphylactises against goat milk; but more definitely still does ewe milk anaphylactise against cow milk, whilst bitch milk does not anaphylactise against cow milk.

Besredka has shown that the casein separated from whey can induce anaphylaxis either on *preparatory*, or *exciting* injection; that whey itself, and the albuminoid substance lacto-protein in whey, precipitated by soda-compounds, are also active.

Other interesting facts have been observed by Besredka, as that the albuminoid from whey may produce anti-anaphylactic vaccination, even by oral administration or by rectal absorption, although sensitisation is never produced through the digestive tract by milk. Sensitising and toxic properties do not disappear on heating milk to 120° for fifteen minutes.

But heated to 130° milk no longer retains its sensitising power, although it continues to preserve its vaccinating power. Therefore the properties of milk can be dissociated by heating to 130°: the vaccinating property is thermostable, and the toxic and sensitising properties thermolabile.

3. *Eggs.* — Anaphylaxis can be produced by egg albumen, and, as in the case of milk, it is specific, but its specificity is not absolute.

Rosenau and Anderson have shown that, in the guinea-pig, turkey egg is anaphylactising to hen egg, and conversely. On the contrary, duck egg is practically harmless to guinea-pigs previously injected with hen egg, nor is the converse true (?)

Ed. Lasné and L. Dreyfus have shown that rabbits anaphylactised with white of hen egg are not sensitive to a second injection of cow milk, horse serum, or even of white of duck egg. But anaphylaxis only remains a specific reaction if the number of *preparatory* injections is limited. If these are many, rabbits react indifferently to later injections of differing albumens.

4. *Toxins.*—In relation to toxins a new element, namely immunity, must be taken into consideration. Since my earliest experiments with the congestines of actinaria, I noted the parallelism of immunity and anaphylaxis, and I concluded that anaphylaxis is the earliest stage of immunity. While seeking a biological reason for, and, if I may say so, the final cause of anaphylaxis, I was led to suppose —it seems less probable to me to-day— that animals acquire this extraordinary sensibility in order to be able, during the anaphylactic period, to resist any further effect of the poison. With certain substances, as, for example, mytilo-congestine, anaphylaxis diminishes markedly

towards the fortieth day, and the state of immunity establishes itself.

Doerr and Raubitschek have observed the same phenomenon with eel serum. The simultaneousness of anaphylaxis and immunity in the injected animal leads to a curious result. If a fresh animal, and one previously injected, be given the fatal dose of crepitine, as crepitine only kills in from ten to twenty days, and a first dose never produces immediate effects, the fresh animal is not affected by the injection; it remains bright, alert, and does not seem to have received the least trace of a toxic substance. But the anaphylactised dog is extremely ill; it passes bloody motions, and suffers from vomiting, ataxy, and mind-blindedness, so much so that it appears to be dying. But frequently it recovers, and the next day appears in almost as good condition as the other dog. After ten or twelve days the latter becomes cachectic, paralysed, and wretched, and dies; the anaphylactised and not immunised dog in the meantime gains perfect health.

This experiment, although apparently paradoxical, is absolutely beyond doubt, and I have repeated it a great number of times. (See Physiological Lab. Rep., 1902, v. p. 514.)

It may be explained without difficulty by supposing that there are formed simultaneously in the blood antitoxins for immunity and toxigens for anaphylaxis. This has since been noted by Doerr and Raubitschek with eel serum.

Contrary to what is observed after the injection of serum a relatively strong dose of toxin is necessary. Doses of congestine below 0·001 gramme do not anaphylactise, but this amount is quite enough to induce anaphylactic symptoms. It is true the experiments were performed on dogs, whilst those with serum were mostly performed on guinea-pigs. But I am sure that the *preparatory* dose of toxin in the guinea-pig ought to be as strong as the *exciting* dose, so that this difference between serum and injected toxins depends upon the antigen injected and not on the type of animal into which the injection is made.

It is certain that, when they have been systematically studied, there will be found to exist great differences, according to their nature, between toxins.

Only to refer to those I myself have studied, mytilo-, actino-, and crepito-congestine, anaphylaxis to mytilo-congestine, for example, disappeared towards the sixtieth day. In the case of actine and crepitine, not merely has anaphylaxis not disappeared on the sixtieth day, but it has become more intense. Even on the one hundred and fiftieth day it is still very strong to crepitine, but the symptoms which develop have not a similar character.

5. *Bacterio-anaphylaxis.*—It might be supposed *a priori* that bacterial albumins, toxins, endotoxins, secreted by micro-organisms, would produce anaphylactic phenomena. As a matter of fact experiments are very clear and demonstrate indisputably that there is a bacterio-anaphylaxis. We will not here refer to sensitivity to tuberculin which deserves separate consideration.

Bacterio-anaphylaxis was first observed by Wolff Eissner, then by Rosenau and Anderson, and by Kraus and Doerr with great precision. It is important, in the first place, to distinguish two very different groups of cases.

(1) There can be extracted from micro-organisms, or from the fluid medium in which they have been cultivated, a toxin which will serve equally well for pre-

paratory or exciting injection; (2) guinea-pigs can be inoculated with a virulent micro-organism giving rise to toxins which replace the *preparatory* injection, and they can then be injected, as an *exciting* injection, with the sterilised culture medium of the same micro-organism. The first method is of easy application. Either cultures sterilised by heat, or toxins precipitated by alcohol and dried, or the sterilised micro-organisms themselves (endotoxins), can be injected. The results are invariably positive—that is to say, the animals present phenomena of intense anaphylaxis when reinjected from twenty to twenty-five days after the preparatory injection. If, instead of injecting a sterilised culture as a preparatory injection, living micro-organisms are injected, the ultimate injection of a culture gives the same results as if the toxin had been injected in preparatory injection as an antigen.

The following is Doerr's description of the effects of bacterio-anaphylaxis: "Cultures on agar are mixed with a 10 per cent. salt solution, allowed to stand for twenty-four hours and then injected into the jugular vein. The guinea-pigs are affected with intense dyspnœa; they fall on one side in less than a minute in a condition of deep coma, passing urine and fæcal matter, and die at the end of five or ten minutes after several deep asphyxial inspirations."

According to Doerr, bacterio-anaphylaxis is strictly specific, so much so that we may hope (as he does) to be able to distinguish the nature of certain nearly related microbial infections by this means. Like animal poisons, bacterial poisons injected into the blood lead to the simultaneous production of immunity and anaphylaxis—that is to say, they induce the formation of antitoxins for immunity and toxigens for anaphylaxis.

Kraus and Doerr have demonstrated this by inoculating guinea-pigs with the bacillus of dysentery, and then giving on the twentieth day in one case an injection of the culture medium in which there was only soluble toxin, in another an injection of the culture on agar which contained both the endotoxins and the organisms themselves. Now the injection of the toxin does not produce anaphylaxis, although it leads to the formation of antitoxins in normal guinea-pigs; consequently the antigen which leads to the production of antitoxins is not the same as that which induces anaphylactic symptoms.

It has also been shown that the serum of infected animals injected into normal animals induces passive anaphylaxis in the latter. Delanoé has studied typhoid anaphylaxis, and has constantly observed it on injecting cultures of Eberth's bacillus either into the peritoneal cavity or under the skin. Its specificity is not absolute; for guinea-pigs sensitised with this bacillus react slightly to *B. coli communis* and the paratyphoid bacillus. Anaphylaxis has not disappeared at the end of four months. It coincides with immunity. Immunity or anaphylaxis is observed according to the strength of the *exciting* injection, immunity following weak doses and anaphylaxis following strong doses. A very intense anaphylaxis is observed even with a sixth of a fatal dose.

Delanoé also tried to settle an interesting but obscure question. On injecting the serum of anaphylactic guinea-pigs, why does the anaphylactic state develop in response to the organism itself and not to the soluble toxins. It appears that guinea-pigs thus injected are more sensitive than the others to bacilliary inoculation, but, as Delanoé points out, this selection is not altogether confined to anaphylaxis, and in addition the results are not absolutely clear. Ascoli attempted to apply this idea to the diagnosis of typhoid fever.

6. *Extracts of Cancerous Tumours.*—Anaphylaxis by injection of cancerous tumours, although *a priori* very likely, has not yet been definitely demonstrated.

Yamanouchi took cancerous mice (Ehrlich's and Michaélis' carcinomata) and injected an emulsion of the same tumour into them. They reacted immediately, showing very definite symptoms, bristling hair, immobility, and in many cases dying within twenty-four hours. Such an injection into normal mice is without effect.

These results have not been confirmed by Apolant, who, using the same technique on cancerous mice, has not observed the results described by Yamanouchi.

H. Pfeiffer and J. Finsterer endeavoured to discover if the juice of cancerous tumours injected into guinea-pigs induced anaphylaxis against this same cancerous juice. They considered the injection of cancerous juice to be equivalent to an injection of blood from anaphylactised animals (passive anaphylaxis). They obtained some interesting results. Although normal guinea-pigs showed no reaction to the first injection of cancerous juice, prepared guinea-pigs reacted definitely to a second exciting injection separated from the first by an interval of forty-eight hours, as in the case of passive anaphylaxis. Possibly by such a procedure we may yet be able to diagnose the actual nature of the tumour. Thus for cancerous tumours as for bacterial infections anaphylaxis would appear to be a valuable means of diagnosis.

I cannot enter here into the details of this interesting question. But I will draw attention to the experiment of Dungern and Coca, who observed a hare tumour inoculated into a rabbit induce a progressively increasing local reaction on each successive inoculation. Dungern also ascertained that by making an extract of a human cancerous tumour and injecting it into the individual from whom it was obtained, a well-marked reaction is induced, whilst this same extract injected into other individuals, even though they be cancerous, produces no effect. (See also Ranzi.)

I also carried out some experiments in this direction, but with entirely negative results. By making an aqueous extract of human cancerous tumours of the breast and precipitating the solution by alcohol, a protein substance, soluble in water, is obtained which can be purified by successive precipitations. This substance has been injected into cancer cases by Ed. Lesné, and has not produced any reaction even in relatively large doses.

Nevertheless it is rational to suppose that anaphylactising substances will be found in cancerous tumours.

7. Chauffard has been able to induce symptoms of anaphylaxis by the injection of fluid from hydatid cysts. This hydatid anaphylaxis probably explains certain grave symptoms observed by physicians after puncture of hydatid cysts. This question has been further studied by Weinberg, Boidin, and Laroche. Although the anaphylaxis may not be very severe, nevertheless it allows definite conclusions to be drawn.

CHAPTER VIII

PASSIVE ANAPHYLAXIS

In the paper first describing anaphylaxis, which I published in 1902, it was stated that anaphylaxis is due *to the production of substances which, with the toxin, form exceedingly poisonous combinations.* Later Pirquet and Schick, without however giving actual proofs, presumed that there is a specific antibody. Nicoll, more definitely in 1906, expressed the opinion that anaphylaxis is a *property transmissible by serum—that is to say, it is linked with some specific substance.* A few months later (February 25, 1907) he carried out actual experiments on the transmissibility of anaphylaxis by serum. But, in order to obtain passive anaphylaxis, he made a large number of successive injections into rabbits (twenty-nine, fifty-one, and twenty-five injections respectively into three rabbits), so that it might legitimately be asked if some substance is not formed in the blood of the animal from which the serum was taken, or if there might not be an accumulation of antigen itself in this animal's serum, *seeing that the same animal received fifty-one or twenty-nine or twenty-five preparatory injections.*

Very shortly afterwards (April 20, 1907), as the result of studying emeticising doses, I stated my conclusion that *after a single preparatory* injection the serum of an injected animal was capable of anaphylactising a fresh animal, and I expressed myself thus:

"The injection of the serum of anaphylactised dogs into normal dogs induces an anaphylactic state in the latter, as if it contained the toxic substances facilitating the action of the poison."

In a more detailed paper, which appeared in July 1907, I described the experiments carried out in the previous February, March, and April, and I included the following typical example:

"A dog which twenty-four hours previously survived an injection of the serum of an anaphylactised dog received 0·047 gramme of actino-congestine, a dose absolutely insufficient to lead to a fatal result or even to serious symptoms in a normal dog. It immediately became extremely ill. On receiving 0·01 gramme it vomited; on receiving 0·04 gramme it rolled over on its side, breathing badly; dyspnœa developed, and it was unable to remain on its feet. It died on the morning of the third day, having survived forty hours. . . . This experiment alone is sufficient to prove that the serum of anaphylactised dogs contains substances which produce anaphylactic phenomena."

Unaware of these results, Gay and

Southard in America, and Otto in Germany demonstrated the existence of passive anaphylaxis a little later. (Gay and Southard, "On Serum Anaphylaxis in the Guinea-pig," *Jour. Med. Research*, xvi., May 1907, p. 143; Otto, "Zar Frage du Serumemffindlichkeit," *Munch. Med. Woch.*, No. 34, 1907.)

In the following years a large number of papers on passive anaphylaxis were published, and now it is a definitely established fact.

I will briefly point out some of its characteristics. For simplicity's sake I will call the substance, as yet not isolated, but present in the serum of anaphylactised animals, *toxigen.* It is practically the same as the substance Gay and Southard called *anaphylactin* and Besredka, *sensibilisin.* But the word toxigen, besides having been given to this substance first, has this further advantage, that it indicates the essential fact of passive anaphylaxis—that is to say, that toxigen without being toxic itself can give rise to an exceedingly powerful poison on coming into contact with antigen. The experiments in connection with anaphylaxis *in vitro*, which I shall presently describe, will show definitely that this is no hypothesis but a fact.

The conditions governing the effective dose of the anaphylactised serum are a little different in the dog and the guinea-pig.

Thus in the case of dogs, the preparatory injection must contain a considerable dose of antigen, at least 0·001 c.c. of congestine or crepitine, and the quantity of serum must be correspondingly strong. Of eight animals which received blood from anaphylactised dogs and immediately afterwards were given a dose of congestine, not fatal to a fresh animal, two only survived—those which had received 2·6 c.c. of serum per kilo. All the others died; even one which had received only 4·5 c.c. of anaphylactised serum dying two hours after receiving the injection.

This is not exactly the same as in the case of the guinea-pig naturally, since the latter is sensitised by extremely small doses of horse serum while appreciable quantities, at least 0·0005 c.c. per kilo., are necessary to sensitise dogs. But it will always be easy to estimate the minimum dose of serum from an anaphylactised guinea-pig which can transmit passive anaphylaxis to a fresh guinea-pig.

At least twenty-four hours must elapse, according to Otto and others, before anaphylaxis can be transmitted from one guinea-pig to another (Gay and Southard, Friedmann, &c.).

As I have not carried out any experiments on guinea-pigs in this connection, I won't venture to question this statement, but in the case of the dog by the injection of a toxin which acts as an antigen, the transmission of passive anaphylaxis is immediate. I have observed passive anaphylaxis already well marked at the end of two hours in the case of a dog. Besides, the best proof that passive anaphylaxis may be immediate lies in the fact that anaphylaxis *in vitro* can be brought about at once on mixing the serum of an anaphylactised animal with antigen, an immediate anaphylactic reaction then being obtained.

If, as we must suppose, anaphylaxis is the result of the chemical combination of two bodies, one a substance existing in the serum of anaphylactised animals (toxigen), the other toxin or antigen, it will easily be understood that in passive anaphylaxis no incubation period is necessary. The incubation period is, in the animal receiving the toxin, *the period during which the toxigen is formed.* Once it is formed and since, in passive anaphylaxis, it is transmitted by the serum, there is no necessity for an incubation period.

Otto, who has studied passive anaphylaxis very fully, believes that after a guinea-pig is sensitised three periods follow which present the following features:

1. The animal is not anaphylactised and its serum does not transmit passive anaphylaxis.

2. The animal itself is not yet anaphylactised but its blood is capable of transmitting passive anaphylaxis.

3. The animal is anaphylactised and its blood is capable of transmitting passive anaphylaxis.

The second period is clearly the most interesting and at the same time the most difficult to understand. It might be explained by supposing that the passage from antigen to toxigen is gradual and that a series of intermediate bodies is formed, whose natural evolution results in toxigen. Probably in these cases the reaction of an animal which received an injection of anaphylactic serum ought not to be immediate as it should be when the serum contains toxigen.

It is important to know if animals, which have received an injection of serum obtained from animals, as yet not anaphylactised but already capable of transmitting passive anaphylaxis, immediately react to an exciting injection, or, as is more probable, if they also require an incubation period.

Otto further stated, and I have clearly and repeatedly confirmed his statement, that there are very great individual differences in the sera of animals treated in exactly the same manner.

The period during which passive anaphylaxis persists is uncertain. I have seen it last twenty days, Gay and Southard fifteen days, and Otto thirty.

But all these are far from being the maximum period; very probably it lasts a long time. It certainly should vary with the antigen injected and the type of animal experimented on.

Passive anaphylaxis has been observed in the dog, the rabbit, and guinea-pig. In the dog it does not merely manifest its presence by immediate effects but also by chronic secondary effects. Occasionally the dog is not very ill after the *exciting* injection; nevertheless it dies sooner than a normal dog and as the result of weaker doses.

The specificity of passive anaphylaxis is well established; but its limits have not yet been defined. It is neither as absolute nor as restricted as was at first believed. Further experiments, both minute and difficult, must be made on these points.

Passive anaphylaxis induced by the injection of sera from the same animal is called homogeneous and passive anaphylaxis induced by the injection of the serum of different animals is called heterogeneous. In other words, if horse serum be injected as a preparatory antigen into a rabbit the serum of this rabbit will anaphylactise a rabbit into which it is injected (homogeneous passive anaphylaxis). But, if it be injected into a guinea-pig, will the guinea-pig be anaphylactised against an *exciting* injection of horse serum (heterogeneous passive anaphylaxis)?

This is an interesting problem, for if the answer were in the affirmative, it would permit the presumption that the anaphylactising substance (toxigen) is more or less identical in different animals.

Now heterogeneous passive anaphylaxis is a reality. Doerr believes it is constant, and he quotes his own experiments and those of Friedberger as proofs. Novotny and Schick did not observe it on injecting guinea-pigs with human blood—the serum of children who had been given injections of horse serum. Among twelve such guinea-pigs only two were sensitive to horse serum. Heterogeneous passive anaphylaxis may be obtained by passing from the rabbit to the guinea-pig but not from the guinea-pig to the rabbit. Friedberger has succeeded in transmitting it from mammals to birds, and inversely.

Doerr declares in this connection that generally speaking the rabbit is not very suitable for experiments in connection with anaphylaxis. Its sensibility varies much with its age. Referring to Friedberger's experiments, and to Friedemann's, and his own, he concludes that the guinea-pig, all other things being equal, is 400 times more sensitive to anaphylaxis than the rabbit. This does not prevent a rabbit from developing anaphylactising substances to a notable extent in its serum, so that the best method for studying passive anaphylaxis according to Doerr, consists in injecting a rabbit with the antigen, and then taking its serum and injecting it into a guinea-pig, thus conferring the anaphylactic state on the guinea-pig. Sensibility to passive anaphylaxis is, in certain cases, such that guinea-pigs have been made sensitive to an antigen by giving them a preparatory injection of 0·02 to 0·03 c.c. of the serum of a rabbit prepared by a preparatory injection of the same serum.

CHAPTER IX

ON ANAPHYLAXIS *IN VITRO*

NOT only are some animals which have been injected with the serum of anaphylactised animals themselves anaphylactised, but also if the antigen be mixed with the blood of an anaphylactised animal there results an intensely toxic fluid capable of producing immediate symptoms.

I have termed this phenomenon *anaphylaxis in vitro.* I believe I was the first to use the expression, and described the first example in my paper published in 1907 thus :—" 58 c.c. of blood of a dog, anaphylactised with mytilo-congestine, are mixed with mytilo-congestine and injected into a second dog. It is immediately affected, a dose of 0·006 gramme per kilo. making it vomit. A dose of 0·02 gramme per kilo. produces great dejection and a state bordering on coma. After being given 0·045 gramme of mytilo-congestine, it is let loose for observation. It is ill, staggers, and can hardly stand on its feet; it has diarrhœa and its breathing is laboured. There is a striking contrast between its grave state and the state of another dog which received on the same day 0·065 gramme of mytilo-congestine mixed with normal serum and was scarcely ill."

But it was with crepitine particularly that in 1908 I obtained the phenomenon of anaphylaxis *in vitro* quite distinctly. This fundamental experiment may be again described here:

"On the morning of June 18, 274 grammes of blood were withdrawn from a young dog which had received 0·002 gramme of crepitine on April 6, and 0·0114 gramme of crepitine heated to

103° on May 21. These 274 grammes of blood yielded 55 c.c. of faintly-coloured serum which was mixed with 40 c.c. of a solution of 1—1000 crepitine. On allowing the two fluids to remain in contact for about twenty minutes, 95 c.c. of the mixture was injected into a second dog weighing 10 kilogrammes at ten minutes to four o'clock. Following the pretty rapid injection of 40 c.c. of the mixture the animal appeared ill, vomiting and suffering from diarrhœa and rectal tenesmus. On completing the injection of the 95 c.c. it was let loose. It was unable to stand and micturated as it lay on the ground. Its pupils dilated and its eyes became wild-looking. There was absolute mind-blindness and almost complete abolition of reflexes with profound insensibility. The breathing was dyspnœic and asphyxial, the heart's action feeble and very frequent. There was practically no pulse. In short the symptoms of anaphylaxis were perfectly characteristic and such as are observed only in the most distinct cases. Towards evening, about 5.30, the symptoms were less serious, but there was still intense tenesmus and blood in the fæces. The following day it remained very ill and scarcely able to drag itself about. It died on the night of June 19-20. It had been given 0·004 gramme of crepitine, a dose which is only fatal ten to twelve days after its injection."

Occasionally anaphylaxis takes another form. A dog was injected with 0·04 gramme per kilo. of yellow crepitine mixed with serum from a dog anaphylactised forty-five days previously. There were some slight nervous symptoms, but the intestinal congestion was both immediate and intense, so much so that while the injection was being made practically pure blood poured from the rectum.

This is an instructive experiment in another respect, for it shows that in certain instances blood contains at the same time both the antitoxin and the toxigen ; it contains the toxigen because, as in this experiment, the dog immediately, during the actual injection, was seized with a bloody diarrhœa ; and it contains the antitoxin because 0·04 gramme of yellow crepitine, which is always fatal, did not kill. Two days after the injection it was in excellent health.

Intense pruritus may also be produced by the mixture *in vitro* of anaphylactic serum and antigen. A dog received 0·017 gramme of yellow crepitine which had been mixed with the serum of another : at first it did not appear ill ; but one or two minutes after being let loose it was seized with intense itching ; it scraped the ground violently, rubbed its nose with its forepaws, and rolled on the ground, scratching its sides. In other words it was seized with an extraordinarily intense pruritus as if it had been given thalassin, notwithstanding the fact that crepitine never induces pruritus when injected in aqueous solution into a normal animal.

I could quote many other experiments showing that under differing conditions, and very likely depending on the quantity of toxigen in the serum, the reaction of the animal receiving the mixture of serum and antigen made *in vitro* is very variable, extending from a very slight pruritus, a mild form, to a rapidly fatal coma, the acute form. It is well to note that the experiment which is so successful with crepitine is entirely unsuccessful with the congestine of actinaria. But there are sufficient reasons for stating that, using certain antigens, the experiment establishes in an incontrovertible manner the fact that the blood of the anaphylactised animals when mixed with antigen *in vitro* becomes toxic.

I find it difficult to explain the phenomenon except by attributing it to a synthetic poison. The antigen, mixed with the toxigen of the serum, leads to the formation of a new toxic substance which I will call *apotoxin*, the effects of which are entirely different from the effects of the toxin.

The toxic effects of the latter are slow in developing. They only appear at the end of ten days. The effects of apotoxin are immediate, sometimes appearing while the injection is being made and manifesting themselves by vomiting, bloody diarrhœa, coma, pruritus, all of which phenomena are entirely lacking after the injection of the toxin alone.

In like manner nothing is observable following the injection of amygdalin or emulsin. But if solutions of emulsin and amygdalin are mixed, hydrocyanic acid develops and the deadly effect of prussic acid poisoning is seen in the animal receiving the mixture.

Further, this is not a mere hypothesis;[1] it is a statement of fact, and it does not seem to me to be possible to explain the sudden outburst of toxic phenomena on the injection of such a mixture otherwise. Of less importance are the various names given to the substance, inactive in itself, and contained in the blood (toxigen), or to the poison resulting from its union with the antigen (apotoxin); it is clear throughout (1) that the blood of anaphylactised animals is harmless; (2) that it becomes dangerous by mixture with harmless doses of antigen; (3) that the effects of the mixture disclose the action of a new poison, deadly to the nervous system, and differing from both antigen and toxigen.

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[1] M. Wolff Eissner somewhere calls it an obscure theory (?) I must conclude that he does not understand it, which is certainly no fault of mine.

Anaphylaxis *in vitro* can also be effected in rabbits. The following are some of A. Briot's experiments: Equal parts of anaphylactised rabbit serum and horse serum are mixed: the mixture is extremely toxic. One rabbit died two minutes after the injection of 10 c.c.; another ten minutes after the injection of 15 c.c.; another ten minutes after the injection of 5 c.c.; a fourth was very ill after the injection of 10 c.c.; a fifth was slightly ill after the injection of 5 c.c.

Nicolle and Pozerski, using pancreatic juice, record an interesting instance of anaphylaxis *in vitro*. The serum of rabbits which had been treated with pancreatic juice was toxic to guinea-pigs when mixed *in vitro* with pancreatic juice, while it was harmless when not mixed with the antigen. It is important that the serum be fresh for it to be rendered actively toxic by the pancreatic juice.

Friedemann, Friedberger, Doerr and

Russ, Doerr and Moldovan, have observed analogous effects in guinea-pigs, so that the phenomenon of anaphylaxis *in vitro* is well established.

A remarkable fact about it, however, is that it cannot always be induced (at least in the dog). Sometimes the mixture of serum from the blood of strongly anaphylactised animals with antigen is harmless. A very definite example of this occurred in the case of a dog which presented remarkable symptoms of intense anaphylaxis, yet its serum mixed with crepitine did not induce immediate phenomena in a second dog though the dose of crepitine amounted to 0·004 gramme per kilo.

It must therefore be admitted that the quantity of toxigen in the blood is extremely variable; the facts of passive anaphylaxis show this, and further, numerous authorities in various serotherapy institutions who prepare horses for the supply of antitoxic serum know well that, though using absolutely identical methods for this purpose in different animals they yield highly variable antitoxin.

The same is true of toxigen. Moreover it may be admitted that toxigen is fixed in some organic tissue and only appears in the blood when in great excess. Apparently it becomes localised in the cerebral tissue, and it is obvious that in certain cases there is too little in the brain for it to be diffused in the blood though there is enough to cause the animal to react to an *exciting* injection.

In 1909 I stated "that if the experiment is only rarely successful it is usually because the toxigen in the blood is insufficient. Most likely it only appears in the blood when there is great excess in the cerebral tissues, for in all probability the toxin injected into the blood is fixed in the brain, to disappear slowly and be transformed into toxigen. Toxigen can therefore be considered an endotoxin fixed in the cells, especially in the nerve-cells, and it is suddenly transformed into extremely toxic apotoxin at the moment the toxin comes into contact with the cerebral cells."

I have attempted to extract this toxigen from the cerebral cells, and have succeeded in a few definite cases.

Having bled a dog to death the cerebral vessels were washed through the carotid so as to clear the brain of all the blood it contained. The brain was then removed and ground up with sand into a homogeneous mass. When well ground up and mixed, three times its volume of saline solution was added to the pulp; the two were mixed as thoroughly as possible; the mixture was centrifuged and filtered ten or a dozen times until the opalescent filtrate passed as easily as water through thin filter paper folded many times. I assured myself that the injection of this cerebral fluid did not lead to symptoms. Different dogs received 110 c.c., 90 c.c., 68 c.c. without showing any effect. But its injection, when mixed with an antigen, produced very distinct symptoms of anaphylaxis.

Anaphylaxis *in vitro* was very definitely obtained with the serum of a dog which was given yellow crepitine thirty-five days previously. While an injection of a mixture of its serum with crepitine was being made into a second dog practically pure blood poured from the rectum of the latter. The liver tissue of the first mixed with crepitine produced no effect on another animal, but its cerebral tissue mixed with crepitine led to immediate symptoms in the animal into which the mixture was injected: dyspnœa, forced respirations, mind-blindness, nystagmus, dilated pupils, tenesmus, diarrhœa, bloody motions, inability to move, followed by staggering and vertigo and almost complete insensibility. In another the injection of the cerebral tissue of a dog mixed with crepitine did not produce immediate notable symptoms, but a half an hour later very serious symptoms suddenly developed and the animal died in a few hours with profuse bloody diarrhœa and in a state of semi-coma.

Lastly, in a third case, the cerebral tissue of a dog anaphylactised two and a half months previously was mixed with crepitine, and the injection of the mixture in the small dose of 2·5 c.c. brought on very grave symptoms, coma, inability to move, and diarrhœa; 5 c.c. of the same cerebral fluid injected into another dog, but without the addition of crepitine, led to some motor trouble lasting fifteen to twenty seconds, but at the end of half a minute there was no trace of this, while for two hours the other dog lay on its side in a paraplegic state and deeply comatose. I have repeated this experiment with slightly different technique; for, in spite of the most careful filtration, it is possible that the cerebral fluid thus obtained is not entirely harmless in itself, though I have injected large quantities into normal dogs without producing symptoms. I therefore took the brain of a dog which had been well anaphylactised and whose blood mixed with an antigen had definitely given the anaphylactic reaction *in vitro*, and I injected it firstly, mixed at once with a harmless dose of crepitine, into a dog which died in thirteen minutes with such symptoms of acute anaphylaxis as I had rarely seen—asphyxic respirations with intense dyspnœa, and, while the heart continued to beat, blood poured from the rectum. Then, taking what remained of the cerebral extract from the first dog, I precipitated it with alcohol; I washed the alcoholic precipitate in alcohol, recovered it with water, added 0·002 gramme of black crepitine, and injected the mixture into another dog. A few minutes after the injection obvious symptoms of pruritus appeared. It scratched itself where it could, rubbed its nose with its forepaws, and sniffed along the ground trying to rub its nose in the clay.

These are the visible symptoms of mild anaphylaxis and they show that the cerebral extract of a well-anaphylactised dog, precipitated by alcohol and recovered with water, yields a fluid which, mixed with an antigen *in vitro*, induces anaphylaxis. The cerebral toxigen had been therefore precipitated by the alcohol from its aqueous solution and redissolved in water.

It is true that in some other cases I have only had negative results, but this is not surprising; for, as a result of the processes of empirical extraction we are compelled to use, only a small part of the total toxigen is recovered.

Belin has ingeniously confirmed the results of these experiments on the fixation of toxigen by the cerebral substance. The brain of a young guinea-pig, born of a guinea-pig sensitised with ox or ass serum, when pounded with ox or ass serum, produced a fluid which immediately killed fresh guinea-pigs. The brain substance, pounded with water, had no effect. Further the fixation of toxigen by the cerebral cells is also proved by the fact that the liver, thyroid, and suprarenals when mixed with ass or horse serum are innocuous. We may also mention the interesting experiments of Achard and Flandin, who, having made a cerebral extract from the brains of guinea-pigs which had died of acute anaphylaxis, proved that this extract is toxic while the cerebral extract from normal guinea-pigs is not toxic.

Doerr in his admirable analysis of anaphylaxis carefully discusses this question of apotoxin, and he arrives at the almost inevitable conclusion that the simplest hypothesis is that anaphylactogen (that is to say, toxigen) combines with antigen to form a new poison (*anaphylaktisches Gift*), which, in my terminology, would be apotoxin. He refers to the experiments of Friedberger on deviation of complement in anaphylactic intoxication and concludes that proof that there is an anaphylactic poison is established. As to whether this anaphylactic poison or apotoxin is single or multiple he does not say. He remarks, however, that the rapidity with which anaphylactised animals recover, since they pass in a few minutes from a very grave condition to a condition bordering on the normal, has no resemblance to the type of intoxication of most poisons. Moreover various experiments, on which I need not lay stress, lead to the supposition that apotoxin is very unstable and disappears quickly after its formation. (See among others a recent note by R. Turro and P. Gonzalès.)

At all events this theory of a *toxigen* producing an *apotoxin* by combination, which I stated in 1907, seems to-day to be well established and universally accepted.

We shall see later that a close relation, almost a similarity, exists between apotoxin and precipitin (Friedberger). Whatever this relationship may be, the titles toxigen and apotoxin seem fully justified, for they accurately describe in their terminology the essential phenomena of anaphylaxis.

CHAPTER X

THE RELATION OF ANAPHYLAXIS TO FORMATION OF PRECIPITIN AND COMPLEMENT DEVIATION REACTION

ALTHOUGH this is a problem of recent origin it is already the subject of a large number of papers. All its details will not be discussed here, for much remains unsolved and it is still the subject of inquiry. Moreover, it does not appear to possess all the importance that German authors seem to attribute to it. Friedberger maintains that the anaphylactic reaction and the precipitin reaction are analogous. Doerr and Russ, Friedemann, and especially Friedberger and Hartoch in a lengthy paper, insist upon such a relationship between the reactions.

The precipitin reaction is intimately

associated, as is well known, with the disappearance from sera of alexin or complement. Sera deprived of alexin are no longer precipitants. Now, as Friedemann has shown in the anaphylaxis of rabbits against injections of red blood corpuscles, complement disappears simultaneously with the precipitin reaction. From this it may be inferred that these three phenomena: anaphylaxis, precipitin reaction, and deviation of complement are definitely related to one another. In rabbits immediately after the *exciting* injection, alexin disappears or diminishes, and this condition persists for twenty minutes. According to Sleeswig it disappears more slowly. A further fact which becomes evident as the result of Friedberger and Hartoch's experiments is that deviation of complement is more marked in passive than in active anaphylaxis; although anaphylactic phenomena are more intense after active than after passive anaphylaxis. These workers concluded that disappearance of the complement, though it has some relation with anaphylaxis, is not due to the same cause.

Friedberger and Hartoch endeavoured to prevent deviation of complement, and for this purpose they used the method of saline injections. With weak doses there was no result; but following very strong doses, that is to say, 1 c.c., 1·5 c.c., and 2 c.c. of a saturated solution of sodium chloride injected into four guinea-pigs weighing 200 to 280 grammes, there was no anaphylaxis.

Though the results of this experiment were positive, I think it is unwise to conclude that absence of anaphylaxis is due to non-disappearance of alexin. As a matter of fact the injection of as much sodium chloride as 0·25 gramme per kilo. is sufficient to affect all the delicate chemical reactions of an organism considerably. It alone will lead to the simultaneous disappearance of both alexin and anaphylaxis without necessarily attributing absence of anaphylaxis to persistance of alexin. This is also Besredka's opinion.

Sleeswig has clearly pointed out that the *exciting* injection in sero-anaphylaxis invariably hastens the disappearance of complement; and he records experiments, performed in 1909, in which he demonstrated this fact to Friedberger. The question of priority is unsettled and besides is of no great interest.

The relation between anaphylaxis and formation of precipitin is no longer in doubt, as the experiments of Scoot show. It was very close in each of thirty rabbits he had under observation.

Many objections have been raised to Friedberger's hypothesis that anaphylaxis was due to the formation of a precipitin *in vitro;* but they have been dispelled to some extent by Doerr and Russ's, and especially Doerr and Moldovan's, important observations that the methods hitherto used to identify a precipitin were imperfect. They conclude:

1. That when there are small quantities of precipitin in a serum its presence cannot be revealed by ordinary methods, so that we are entitled to call in question any observations in which a non-precipitant serum has been credited with anaphylactic properties through passive anaphylaxis.

2. That even with a very weak precipitant reaction passive anaphylaxis may be seen simultaneously with the disappearance of complement.

3. That anaphylaxis after injections of red blood corpuscles may be observed in the guinea-pig and dog. There is some similarity between the cytotoxic action of sera and anaphylaxis.

The important point in these researches

is the actual study of the resultant precipitate. Doerr and Russ have shown that it is toxic. Friedberger, by treating it with guinea-pig's serum, rich in complement, obtained a toxic product which was not isolated in solution in the serum. It was called by him anaphylatoxin and killed guinea-pigs with all the symptoms of acute anaphylaxis. This anaphylatoxin of Friedberger seems to be identical with the substance I called apotoxin. At the same time the complement when brought into contact with the precipitate from precipitin disappears, consequently Friedberger gives the following explanation. The resultant precipitate placed in serum rich in alexin, is the source of anaphylatoxin. According to him therefore the anaphylactic reaction requires three factors: a precipitating substance, furnished by the antigen; a precipitated substance, furnished by the antigenic serum; and complement, furnished by the normal serum. We shall return to these facts later when considering the theory of anaphylaxis.

Though generalisations must be made with reserve, anaphylaxis in the guinea-pig, in the rabbit, and in the dog is probably not produced under the same conditions and the actual reactions are probably different. Precipitant reactions are perfectly distinct in the rabbit, while anaphylactic phenomena are much less intense than in the dog; on the other hand precipitant reactions are absent or hardly appreciable in the dog. Further, according to Biedl and Kraus, the guinea-pig's reactions to apotoxin or precipitin (Friedberger's anaphylatoxin) are not comparable to those classified as anaphylaxis. Apotoxin or precipitin kills by fibrinous coagulation and the formation of masses of agglutinated red blood corpuscles.

It takes effect even in animals that

have been given atropine, whilst in the classical anaphylaxis of guinea-pigs atropine prevents death. Biedl and Kraus conclude by declaring that Friedberger's precipitin and heterogenic sera do not produce anaphylaxis.

As this difficult question is still a subject of research I purposely refer to it briefly.

CHAPTER XI

ANTI-ANAPHYLAXIS

We owe our chief knowledge of anti-anaphylaxis to Besredka, who perseveringly studied it in particular with success. Previously, however, Rosenau and Anderson had discovered the fundamental fact that guinea-pigs can be protected against anaphylactic symptoms by intra-peritoneal injections of an antigen, horse serum for example, in repeated and massive doses.

But intra-peritoneal injection is unreliable, at least in fresh guinea-pigs, while the effects of intra-cerebral injection are constant and obvious. Besredka demonstrates the following highly important facts :

A second injection of serum given

before the expiration of twelve days is harmless and, further, is vaccinating—that is to say, the guinea-pig which has been sensitised by a first (*preparatory*) injection is not affected by a second (*exciting*) injection made into the brain. Such immunity to anaphylaxis is quickly established in some cases in an hour and a half. Consequently intra-peritoneal injection protects against intra-cerebral injection. In another paper, in which they give these facts further consideration, Besredka and Steinhardt prove that anti-anaphylactic immunity conferred by an injection made in the pre-anaphylactic period may last three months.

Neither the brain, liver, spleen, nor serum can transmit anti-anaphylactic immunity (Besredka).

Besredka explains these facts by supposing that the brain of the sensitised animal is desensitised in the same manner that the guinea-pig's brain, in which tetanic toxin is fixed, loses its tetanic toxin and is disintoxicated as the result of treatment with anti-tetanic serum (Wasserman and Takaki's experiment).

These facts, observed by Besredka after an intra-cerebral *exciting* injection, have been noted by Otto after a subcutaneous *exciting* injection. He demonstrated that the state of sensitisation in guinea-pigs can be brought to an end by injecting them during the pre-anaphylactic period with either massive or repeated doses of serum.

I have been able to demonstrate in the dog by a totally different method something analogous to this anti-anaphylaxis. If an exciting injection of the antigen in extremely weak solution, say 0·1 gramme per 1000, is given to an anaphylactised dog, anaphylaxis is unobservable, or all but unobservable. These results suggested that the first portions of antigen injected in very small quantity developed an anti-anaphylactic state. But it is difficult to interpret the meaning of this experiment, and, moreover, it is possible to explain its results by other hypotheses than anti-anaphylaxis.

Besredka has also carried out a series of interesting experiments to determine the effect of heat on the anaphylactising properties of antigens.

In the first place he confirmed this fact, that heat does not prevent the sensitising antigen from acting, in other words the antigen is thermostable; he calls this antigen which is capable of sensitising guinea-pigs sensibilisinogen. On the other hand this same body heated at 96° for twenty minutes has no action when given in *exciting* injection. This has been confirmed by Kraus and Volk.

In interpreting these facts Besredka considers that the antigen is simultaneously sensibilisinogen and anti-sensibilisinogenic.[1] Heat does not destroy the sensitising power but does destroy the exciting power. On the other hand anti-anaphylactic immunity cannot be conferred by serum heated to 96°.

In another paper, Besredka again refers to this double function of sensitising and anti-sensitising and shows that probably it is a property of the same substance. By warming or diluting sera the intensity of one or other function is modified.

In addition to the anti-anaphylaxis due to the injection of weak doses, various chemical substances have been suggested as likely to induce it, but their efficacy, it may be said at once, is not very great.

However Netter has noticed that the injection or ingestion of calcium chloride, one or two days before the injection of serum, considerably diminishes the symptoms of serum sickness. The Dutch physician Gewin has had similar results. But the symptoms following a first injection of serum cannot be compared with anaphylactic symptoms, although there is a definite analogy between them. Besides, from an experimental point of view, calcium chloride is only effectual in antagonising anaphylaxis in extremely strong, almost poisonous doses. In certain experiments undertaken on Netter's suggestion I was unable to demonstrate the slightest diminution in the pruritus brought on by thalassin, even though I used enormous doses of calcium chloride; and the pruritus of thalassin is curiously analogous to that of anaphylaxis.

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[1] These words seem to me rather too euphonical for us to seriously think of retaining them.

Further, the anaphylactic reaction is so delicate that various chemical actions can easily modify it. I have observed a simple injection of water, given two or three days before, greatly diminishing its intensity. Further research should certainly be conducted in this connection.

If Auer and Lewis's theory were accurate, atropine should prevent anaphylaxis at least in the guinea-pig; but this is not uniformly the case, even among their experiments published up to 1910.

As to the action of barium chloride, to which Biedl and Kraus attribute definite anaphylactic properties, it would appear that the question deserves consideration; for the barium salts are such virulent poisons, acting with great intensity on the organism and especially on the nervous system, that they cannot be called true anti-anaphylactics. All poisons of the nervous system, like ether and chloral, in Besredka and Roux's historical experiment, are in themselves anti-anaphylactics; I would preferably call them pseudo-antianaphylactics; they merely prevent anaphylaxis by paralysing the reactions of the nervous system.

CHAPTER XII

ANAPHYLAXIS IN MEDICINE

1. *Forensic Medicine.*[1]—Since the recognition of the specificity of anaphylaxis, its application as a delicate test in the recognition of organic fluids has been considered. Besredka, Uhlenhuth, Thomson, Sleeswig, Pfeiffer, almost simultaneously suggested this simple idea.

The experiments carried out with this object in view, especially those made by Uhlenhuth and Händel, have been very satisfactory. Even minute quantities of a tissue or of an organic liquid injected into a guinea-pig excited a *specific* anaphylactic sensitivity. These authors were able to use the flesh of a mummy three or four thousand years old; the injection of such human tissue into guinea-pigs rendered them sensitive to human serum and to human serum alone.

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[1] See H. Pfeiffer's *Das Problem der Eiweissanaphylaxie*, Jéna, 1910, p. 231.

Small quantities of desiccated blood taken from animals of different species have been identified by the anaphylactic reaction as belonging to such and such a species of animal. Not merely can it be decided in this way whether it is the blood of fish, mammal, or bird that is in question, but even most frequently the kind of fish, mammal, or bird can be told. To what extent these observations may be applied to legal medicine, which requires both accuracy and precision, I will not discuss here. Doerr observed that the anaphylactic method can in most instances be combined with the serum precipitant method.

2. *Diagnosis of Disease.* — We have seen that bacterial poisons induce a specific anaphylaxis. From this fact de-

veloped the idea that an illness could be recognised in many cases by the specificity of the reaction to such and such a toxin. Two processes may be employed for this purpose: in one a subcutaneous injection of a given specific serum is administered to the patient, as for example in the cuti-reaction of tuberculosis; in the second, the patient's serum is taken, injected into guinea-pigs, and two or three days later these are examined to see if they are sensitive to a given bacterial toxin, the reaction then constituting one of typical passive anaphylaxis. So far, from the practical point of view, diagnosis by anaphylaxis has no real value, but there is prospect of its becoming useful.

Omitting tuberculous anaphylaxis which is special and is to be referred to elsewhere, there remain for inquiry the anaphylacto-diagnosis of cancer, the results of which are doubtful or nil, of echinococcus, and typhoid. But it can be foreseen, especially in face of the facts established in connection with tuberculin, that the methods of diagnosis by anaphylaxis will be greatly extended. Possibly other morbid conditions will be disclosed by this means.

3. *Pathogenesis of some Morbid Symptoms.*—There is no doubt that certain morbid symptoms, which hitherto have not received rational explanation, can be interpreted in the sense of an anaphylactic reaction. Firstly, there is the extraordinary sensitiveness of some individuals to certain foods. Egg albumen particularly is extremely toxic to some people, and the cases in which the eating of eggs, even fresh eggs, has produced general symptoms of a grave nature, and acted as a true poison, are innumerable.

In the same way the eating of certain foods : pig meat, hare, strawberries, asparagus, mussels and shell fish, leads in certain people to obvious symptoms.

Hutinel has attributed the cases of gastric intolerance to milk met with among nurslings to anaphylaxis.

There is also a condition of idiosyncrasy which makes some individuals particularly sensitive to the action of a drug, as shown by those urticarial eruptions which develop after the administration of salicylates, quinine salts, or iodoform, &c. Probably all idiosyncrasies depend upon anaphylaxis.

Chauffard, in his studies of hydatid anaphylaxis, attributes cases of sudden death, following upon a certain quantity of cystic fluid reaching the peritoneum, to anaphylaxis ; and he has strengthened this perfectly rational opinion by ingenious experiments made with hydatid fluid.

Rosenau and Anderson state that puerperal eclampsia may, in some cases at least, be explained by anaphylaxis. Hay fevers, specific asthma, are possibly due to the same cause. It has also been suggested as the cause of sudden death in certain cases of cancer attributed to emboli, a diagnosis made because no other cause could be found, but in which no migratory clot was discovered.

As to the symptoms following second injections of serum, they evidently are phenomena of true anaphylaxis. This point has been extensively studied by physicians and I do not discuss it even briefly here. It will be sufficient to mention that the symptoms of serum sickness are directly comparable to the symptoms of anaphylaxis in animals.

4. *Concerning Anaphylaxis in Tuberculosis.* — At the beginning of our researches on anaphylaxis in 1902 we pointed out the analogy that existed between anaphylaxis and the sensitiveness of tuberculous animals to tuberculin.

Koch's excellent work, confirmed by several investigators, showed that a normal animal does not react to tuberculin, whilst tuberculous animals react to a thousand times weaker doses. To what is this enormously increased sensibility due if not to anaphylaxis? But the moment that precision in detail was sought wide difference developed. In fact a first injection of tuberculin did not seem to sensitise normal animals to a second injection. The blood of tuberculous animals did not seem to confer passive anaphylaxis. In short the anaphylactic reaction generally resulted in an abnormally low temperature, whilst the injection of tuberculin into tuberculous animals invariably led to an abnormally high temperature. Such practically was the position of this question from 1902 to 1907. But from this time many workers, more systematic than their predecessors, have shown that tuberculin, with certain important differences, behaves like an albuminoid antigen—that is to say, it induces the anaphylactic state like albuminoid antigens after a preparatory injection. We are not able to enter here into a detailed history of this special anaphylaxis ; a few brief references must suffice. The first and most important point is to know if the injection of tuberculin is *preparatory ;* in other words, it is important to know if tuberculin anaphylactises to tuberculin. Now the results of experiments on this point are extremely variable. But it would seem that intra-cerebral inoculation, in *exciting* injection, induces a very early reaction in animals which are non-tuberculous but have received a *preparatory* injection of tuberculin (A. Marie and Al. Tiffeneau ; Slatineanu and Daniélopolu). The last-mentioned authors have published the following experiments among others :

Two guinea-pigs received 1 gramme

of tuberculin, two others 0·1 gramme of tuberculin; at the end of thirty-two days they received an intra-cerebral injection of a small quantity of tubercle bacilli. Both sets died in four days: the two inoculated at first with 1 gramme in twelve hours, and the two inoculated with 0·1 gramme in four days. I confess that this experiment is not quite convincing; for the *exciting* injection was not made with the same tuberculin, but with tubercle bacilli. So that the conclusion to be drawn amounts to this: in spite of every effort made up to the present to obtain anaphylaxis from tuberculin to tuberculin, no one has succeeded as yet in inducing it constantly, although the reaction of tuberculous men or animals to tuberculin is intense and acute. This is certainly an anaphylactic reaction, for it leads either to a local ophthalmo-reaction, cuti-reaction, or to a general reaction with fever, pulmonary congestion, coma, dyspnœa, &c. It follows that the *exciting* substance here — tuberculin — contains the necessary elements to produce the anaphylactic reaction, but this *exciting* substance cannot also play the part of a *preparatory* substance.

We saw previously, while considering the action of actino-congestines and crepitines, that this was also true of a great number of antigens in which the *preparatory* property, that is to say the *preparatory* substance, and the *exciting* property, that is to say the *exciting* substance, could be dissociated. Consequently in an animal infected by the tubercle bacillus, the infection gives rise to substances which are *preparatory*, but which are *not present in the tuberculin we use* either because they have not developed in the culture media with the same intensity and the same ease as in the infected organs or rather because processes in the preparation of tuberculin like filtration, precipitation by alcohol, heating to 200° alter the *preparatory* substances. So that we find, in the various kinds of tuberculin, an efficient *exciting* substance but no *preparatory* substance, a fact in no sense paradoxical.

Yamanouchi studied passive anaphylaxis to tuberculin. Taking the blood of human beings who had died from tuberculosis and injecting it into guinea-pigs he observed that these were sensitive to an *exciting* injection of cultures of tubercle bacilli given intravenously twenty-four hours afterwards. In later experiments he took the blood of guinea-pigs, inoculated with tubercle, and injected it into rabbits. The rabbits thus injected were given an *exciting* injection of tuberculin, and were found to be sensitive. The guinea-pigs from which the serum was taken only yielded active serum, that is to say serum conferring passive anaphylaxis on other guinea-pigs, if their blood was withdrawn four weeks after the injection. Up to this time, even if anatomical lesions are present, their blood does not confer passive immunity on guinea-pigs.

Other workers have also made important contributions to this question of passive anaphylaxis in tuberculosis, notably Ed. Lesné and L. Dreyfus. Guinea-pigs which had been given serum from human tuberculous individuals received an intra-cerebral inoculation of tuberculin. Out of one hundred so inoculated, twenty reacted; while among normal guinea-pigs injected with normal human serum, only 5 per cent. reacted. By using as a preparatory injection cerebro-spinal fluid from tuberculous individuals they obtained in guinea-pigs a positive reaction to tuberculin in 33 per cent. cases.

Ed. Lesné and Dreyfus rightly conclude that this proportion, 20 per cent. to 33 per cent., is too low to permit an anaphylacto-diagnosis of tuberculosis, and that further researches are necessary.

The later negative experiments of Marelli, Joseph, and Simon, and the positive experiments of Helmholtz, show that this question ought to be further inquired into by other methods. It is no less true that the reaction of tuberculous individuals to tuberculin is an anaphylactic phenomenon, and everything suggests that by proper methods both the *preparatory* substance which does not exist in tuberculin but exists in the different organs of the tuberculous individual, and the *exciting* substance which is obviously present in tuberculin, will sooner or later be separated from tuberculous products.

It is futile to insist upon the great importance which the discovery of these two substances will exercise on the diagnosis and treatment of tuberculosis. All we have stated about tuberculosis and tuberculin is also applicable to glanders; but there are as yet no definite experiments on this subject.

CHAPTER XIII

LOCALISED ANAPHYLAXIS

Localised anaphylaxis, that is to say the increase in sensibility after a second injection in the tissues situated in the neighbourhood of a first injection, was observed by Arthus in the rabbit. He has not been able to demonstrate it in the dog, rat, pigeon, guinea-pig, or duck, so that up to the present localised anaphylaxis is hardly recognised except in rabbits.

As observed in the rabbit by the swelling, heat, and œdema at the site of the first injection, after the administration of an *exciting* injection, it does not appear to me to be specific; for sero-anaphylactised rabbits are locally sensitive to an *exciting* injection of peptones; and rabbits anaphylactised by peptone are locally sensitive to an *exciting* injection of gelatine.

But although local anaphylaxis may not be specific, there is, from the point of view of the local as from the general reaction, a scale of toxicity. Horse serum produces, in all animals examined, even in those anaphylactised with gelatine and peptone, a more intense reaction than do gelatine or peptone. Peptone induces a reaction more lasting than gelatine.

So that, as all other experiments have shown, the rabbit presents a very different type of anaphylaxis to that observed in other animals.

It is certain that a localised anaphylaxis can be demonstrated in man, inasmuch as physicians have observed it after second injections of serum. The second injection occasionally excites sensitivity and redness at the point at which the first injection was made. In any case, the local reaction to the second injection is always much stronger than it was to the first injection. Frequently it is the only effect observed. Of general symptoms there are none or practically none, and they are confined to phenomena of œdema, swelling, redness, and pruritus at the site of injection.

The curious experiments performed by Yamanouchi in 1909, comparing the excitability of the nerves in rabbits which had received preparatory injections of ox or horse serum, evidently resembles localised anaphylaxis. He found that in rabbits prepared with ox serum, a nerve impregnated with ox serum becomes less excitable, although its excitability is not modified when it is bathed with horse serum, and inversely.

All these facts suggest that the toxigens diffuse themselves throughout the organism, while they seem to localise themselves more particularly in the brain and serum.

Landouzy has recently studied an interesting form of localised anaphylaxis—namely, that special condition of joints into which a certain quantity, apparently harmless, of tuberculin has been previously injected.

C. Demel has proved that the hearts of rabbits anaphylactised to egg albumen were more sensitive than the hearts of normal rabbits to the action of a serum containing egg albumen. But this is not localised anaphylaxis in the strict sense of the word.

CHAPTER XIV

CHRONIC ANAPHYLAXIS

THE essential character of the anaphylactic reaction is its rapid disappearance. One of two things happens: either the animal dies in one or two hours at the most, or it definitely survives. At least this is what seems to occur in guinea-pigs and rabbits when the *exciting* injection is made with a slightly toxic and almost harmless substance, like an heterogeneous serum. But, in dogs treated with toxins in second injection, although the second injection be a dose well below the fatal dose, *the animal recovers from the anaphylactic shock*, but it dies ten, twenty-four, or forty-eight hours afterwards. Such chronic anaphylaxis is not absolutely peculiar to the dog, for rabbits, at the end of several successive injections of toxins or even of serum, at length die of cachexia.

In order to explain this slow death of anaphylactised animals, it must not be supposed that the anaphylactic poison apotoxin persists throughout the tissues; for most frequently, in dogs at least, the period of recovery has commenced, showing clearly that in those animals which ought to die slowly, as well as in those which ought to recover, apotoxin has disappeared. The phenomena succeed each other in this order. Firstly, there is the anaphylactic shock, which is violent and leaves the animal for half an hour or an hour in a state of impending death. But, except in very rare instances, death does not follow immediately and evidences of recovery are apparent. The dog gets up, walks about, seems almost cured, although diarrhœa and tenesmus continue. In spite of this apparent recovery, it becomes very weak some hours later; it cannot rise from the ground; it has profuse intestinal hæmorrhages, complete inertia, insensibility, and an abnormally low temperature.

In all probability it dies of lesions visible or invisible produced by the apotoxic poison. *Sublata causa non tollitur effectus.* The injuries to the nerve-cells have been so serious that they cannot return to their normal state, although the poison affecting them has disappeared.

CHAPTER XV

ALIMENTARY ANAPHYLAXIS

Rosenau and Anderson were the first to point out that anaphylaxis can be induced by alimentary ingestion. They experimented on guinea-pigs and demonstrated that horse serum, in doses non-toxic to normal guinea-pigs, gave rise to anaphylactic symptoms in guinea-pigs which had been fed on horse-flesh. But the experiment frequently failed and in any case the amount of meat given for ingestion must be considerable. Also some experimenters have been unable to repeat the experiment of alimentary anaphylaxis. Further, certain foods like milk and eggs which inevitably induce the anaphylactic state after intravenous injection, never, or hardly ever, induce it by alimentary ingestion.

Ed. Lesné and L. Dreyfus tried to discover if anaphylaxis could be obtained by direct injection into the portal vein and gave interesting proof that such an injection is equivalent to injection into any vein whatsoever for the purpose of producing the anaphylactic state. They anaphylactised dogs as surely by injecting actino-congestine into the portal vein as by injecting it into the tibial saphenous vein; similarly with the mesenteric vein, which apparently proves that neither the liver nor the intestine affect proteid substances in such a way as to render them non-anaphylactising.

It follows that if ingestion does not induce the anaphylactic state it is not because the hepatic and intestinal glands and lymphoid tissues have altered the albumin, but solely because changes in the materials introduced through the mouth have taken place in the intestinal tract during gastric and intestinal digestion which render them harmless. And as a matter of fact Ed. Lesné and L. Dreyfus showed that the injection of white of egg into the stomach or small intestine of a rabbit, or of actino-congestine into the stomach or small intestine of the dog, does not result in anaphylaxis; while, on the contrary, anaphylaxis does result when the first injection is made into the large intestine.

This led to inquiry into the effects of artificial digestion on albumens considered as anaphylactising substances. In spite of much research work the results are not convincing. However these two facts which seem contradictory should be borne in mind:

1. Alimentary ingestion never or hardly ever induces the anaphylactic state.
2. The products of tryptic or peptic

digestion are very toxic and slightly anaphylactising, although normal digestion entails neither intoxication nor anaphylaxis.

Briefly the effects of artificially digested albuminoids are not fully understood and are variously interpreted. As digestion varies, both in its duration and in the formation of various products, in different species and different individuals, so the ingestion of similar albuminoids may lead to very different results according to the species and the individuals taking them. I carried out the following experiment on nine dogs: three were fed on raw horseflesh, three on milk, and three on eggs. At the end of forty days I tried to find out if they were anaphylactised to horseflesh, milk, and eggs respectively. The special feeding was suspended during the last thirty days in the case of one dog in each series in order to eliminate the possibility of anti-anaphylaxis. The three dogs fed on milk and injected with milk as an *exciting* injection presented no symptom. One of the three dogs fed on egg albumen firstly and later injected with it had transient and mild symptoms of pruritus. Of the three dogs fed on horse-flesh and later injected with muscle serum from horse-flesh, one presented very distinct symptoms of anaphylaxis—great fatigue, with prostration and inability to walk. Further it gave this very characteristic phenomenon of anaphylaxis—*recovery actually whilst the injection was being given.* The intensity of the symptom was not increased by decreasing the dose. The various evidences of prostration seemed to disappear gradually after the administration of such an extremely small dose as 0·5 c.c. of muscle serum per kilo. body weight and even when the dose had been increased to 2 c.c. per kilo. body weight. Is it not the inevitable conclusion to be drawn from these experiments that anaphylaxis *sometimes* does develop as a result of alimentary ingestion? Stated in other terms, the intestinal chemical changes which transform the albuminoids and, all else being normal, render them harmless, are not identical in all individuals.

The various symptoms observed after ingestion of different aliments must be attributed to anaphylaxis. Without entering into details, they should nevertheless be referred to here. Some persons as a consequence of taking a certain aliment are known to rapidly develop very serious symptoms occasionally of intense gravity, in appearance at least, such as urticaria, œdema, pruritus, fever, nausea, vomiting, diarrhœa, prostration, and the lipothymic state. Now all these are precisely the symptoms observed in serum sickness following the injection of a second dose of serum.

Such alimentary anaphylaxis is

observed sometimes after eating eggs. Although eggs are an excellent article of diet, they occasionally lead to very remarkable symptoms of individual anaphylaxis. A personal observation in this connection may be quoted:

Lightly cooked yolk of egg even in very small quantities gives me violent gastric pain and occasionally makes me vomit. Shofield (quoted by Doerr) records an extraordinary instance of analogous susceptibility to eggs in a boy aged thirteen; if he swallowed the smallest part of an egg it brought on urticaria and an asthmatic attack. Doerr states that he possesses the same personal susceptibility. (See also Horwitz.) Ed. Lesné quotes the very interesting case of a girl of eight years of age who had not eaten eggs for four months because they disagreed with her and then ate a cream in which were a few eggs. She was immediately seized with very severe symptoms apparently endangering her life. Castaigne and Gouraud quote the case of a boy aged five years in whom a very small amount of yolk of egg brought on intense colic and diarrhœa. Most people however digest eggs well.

Two hypotheses may be referred to in explanation of this individual predisposition: these persons are sensitive either because the normal products of digestion on absorption into the blood recognise an individual who is sensitised and who possesses special toxigens; or because digestion is abnormal and in its course special substances are produced which when absorbed into the blood give rise to symptoms because they are toxic. Strictly speaking a third opinion can be expressed according to which there would be present in an individual, whose blood held certain toxigens, a special sensitivity and at the same time in the same individual an imperfect digestive process permitting the formation of substances prone when present in the blood to react upon the toxigens there.

In the present state of science it is difficult to speak with certainty of any hypothesis. But considering all that is known of the various reactions of different individuals to subcutaneous injection, in which digestive changes take no part, it may be admitted that most likely an anaphylactic state peculiar to such persons does develop.

An experiment of Bruck which should be repeated makes this hypothesis still more probable. He took the serum of a person who could not eat pig meat without showing symptoms of intolerance and injected it into guinea-pigs, who were anaphylactised in this way against pig meat.

Very different aliments give rise, in

certain predisposed persons, to symptoms of intolerance which can provisionally be called anaphylactic. Milk must be specially mentioned. We previously have seen that milk, injected into veins or into the peritoneal cavity or subcutaneously, induces the anaphylactic state by means of the proteids it contains. In exceptional and very rare instances, it does so even when swallowed. Occasionally children are met with who, though breast-feeding suits them admirably, are seized with serious symptoms when put on cow milk. Finkelstein (quoted by Castaigne and Gouraud) reports a case of this nature which ended fatally. Hutinel has recorded cases of absolute intolerance of milk. Some adults are unable to take it without immediately suffering from such symptoms as vomiting and diarrhœa.

A true intoxication, characterised by

fever, urticaria, œdema, rheumatoid pains, diarrhœa, vomiting, and the syncopal state, is brought on in some predisposed people especially by fish, molluscs, and crustacea. The specificity of such intoxications is occasionally very strict. L. Landouzy informed me of a remarkable example: the individual became sick after eating a single very fresh prawn, yet she was unaffected by lobster, crayfish, or other crustacea.

Generally speaking, mussels are borne the worst and it is certain that the mytilo-congestine extracted from them possesses remarkable anaphylactic properties. So that probably it is a question of anaphylactic intoxication rather than of digestive insufficiency permitting the passage of substances insufficiently altered by the digestive juices into the blood.

Analogous symptoms are occasionally produced by eating fish. But it is well to distinguish those which at all times are toxic, those which are occasionally toxic, those which are hardly ever toxic. Those always toxic evidently contain toxins which the digestive juices do not alter and consequently when they are absorbed and reach the blood, symptoms of poisoning appear. These symptoms have none of the attributes of anaphylactic symptoms. As to other fish which are toxic, some occasionally and some very exceptionally, the most rational explanation of their effects seems to be that they are anaphylactic although we have no actual experimental proof in support of the statement.

Alimentary anaphylaxis has never yet been observed as the result of eating fruit, with the exception of strawberries, or vegetables.

A solution of all these problems will probably be found in a short time and in all probability it will be shown that the blood of different individuals varies; generally a toxigen is not present but in exceptional instances a toxigen, capable of reacting to the presence of eggs, milk, strawberries, mussels and other foods, is present.[1]

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[1] Whilst seeing this book through the press, I have proved, by unpublished experiments, that the ingestion of certain toxins like crepitine brings on well-marked anaphylaxis; and also that dogs injected with crepitine are unable one month later to take even a small dose by the stomach without being seized with anaphylactic symptoms.

CHAPTER XVI

GENERAL ANAPHYLAXIS

It may be asked whether or not anaphylactised animals, animals that have been given an antigenic inoculation more or less recently, have not acquired in consequence a sensitivity to toxic action differing from their ordinary sensitivity. In order to demonstrate this sensitivity I used apomorphine, the emetic dose of which can be estimated accurately. Further its action resembles that of such antigens as crepitine and actino-congestine, both of which are definitely emetic, especially the latter. Apomorphine hydrochlorate injected into the peritoneal cavity of dogs in doses below 0·004 gramme per kilo. does not usually produce vomiting, but vomiting is almost a constant symptom after the injection of 0·005 gramme and moreover it is practically the only symptom produced. The dog yawns, stretches itself, and is dejected; sometimes it scratches itself or develops a slight diarrhœa.

My experiments were carried out on a large number of normal dogs to which may be added eight others that were given a non-anaphylactising dose of emetine a long time previously.

Of thirty-six dogs given 1·1 c.c. per kilo. by injection into the peritoneal cavity, the strength of the solution being 0·25 gramme of apomorphine hydrochloride per litre, eight vomited on being given 0·00275 gramme of the salt per kilo. Vomiting began on an average six minutes after the injection was given. Of forty-two normal dogs, or dogs that were not anaphylactised either because the preparatory injection was too recent, less than seventeen days, or too old, over 200 days, twenty-five vomited: 60 per cent. among the latter, and 25 per cent. among the former.

These are merely rough figures; for among the animals given crepitine was one which had received a dose as small as 0·00001 gramme. Another was given a dose of crepitine which had been heated to 103°. Therefore it may be said that among the normal animals the proportion of those that vomited was 8 : 38; while among those which had previously received toxins the proportion was 25 : 40; say 63 per cent. and 21 per cent., representing a considerable difference which has a real significance inasmuch as it is based on the large number of seventy-eight experiments carried out under diverse conditions.

This establishes the essential fact that the vomiting centre in the medulla can be rendered sensitive to the action of any toxic substance even by substances so different as apomorphine and congestine.

Perhaps we have here a clinical method for determining whether a given individual is anaphylactised or not. In any case these experiments settle one point of considerable importance. In the case of the normal dogs vomiting took place four, five, six, seven, and eight minutes after the injection was made into the peritoneum. On the other hand, in the case of the anaphylactised dogs vomiting was greatly delayed in some instances fifty-four, thirty-eight, thirty-seven, thirty-two, and twenty-three minutes after the injection; on an average it occurred in eighteen minutes after the injection in the dogs that were anaphylactised and in six minutes in those which were not.

Apparently there is some secondary process, peculiar to anaphylactised organisms and entirely absent in non-anaphylactised organisms, which only develops in anaphylactised animals after a long delay, as if chemical reactions took place within them more slowly and in any case of a different nature to those which occur in non-anaphylactised animals.

The phenomena of general anaphylaxis concerning which we know little as yet must be studied thoroughly. Up to the present we have been concerned only with specific anaphylaxis. But *general* anaphylaxis, that is the increase of sensitivity—be it ever so light—to *all* poisons as the result of the injection of a single antigen, will possess very great interest and will carry from a practical as well as from a doctrinal point of view, important consequences.

CHAPTER XVII

CONCLUSIONS

THE fundamental feature of anaphylaxis is the modification of the cells of an organism by the injection of a dissimilar albuminoid substance, so that they seem to react with greater intensity on the repetition of the injection.

For this modification of the cell to take place, it is necessary and sufficient that a definite incubation period should elapse between the moment the antigen enters and the moment the cell becomes more sensitive—that is to say, anaphylactised. Once the cell is anaphylactised it retains this property for a very long time, one or two years or more, the time varying both with the receiving organism and the nature of the antigen introduced.

The simplest explanation of this increased sensitivity is that which I gave in 1907 when describing the phenomenon of passive anaphylaxis—that there is produced in the tissues of the receiving animal a substance not toxic in itself but capable of yielding a toxic substance by combination with the antigen.

The existence of passive anaphylaxis has been confirmed by numerous experiments and is now a well-established fact. To understand it, to understand the transmission of the anaphylactic state to a normal animal by the injection of the serum of an anaphylactised animal the presence in the serum of a chemical substance, harmless in itself, but capable of becoming dangerous, must be acknowledged. This particular substance will be called *toxigen*, a word indicating, as its derivation suggests, that it is not toxic itself but is capable under certain circumstances of giving rise to a toxin.

Similarly amygdaline is in no sense toxic when injected into the blood ; but under the influence of a ferment (emulsine) it sets free hydrocyanic acid and becomes toxic. Amygdaline is therefore a toxigen.

This substance has been given other names by different authorities—sensibiline, anaphylactine, anaphylactogen, &c. But to avoid the use of many synonyms, often the source of confusion and error, I propose henceforth to call it toxigen ; this was the title first given, and it appears to me the most suitable.

Another fact which I foresaw in 1907 and actually demonstrated in 1909 made the mode of action of toxigen clear—namely, that the mixture of antigen with serum containing toxigen is immediately toxic. What I called anaphylaxis *in vitro*, the production of an instantly toxic fluid exactly like the instantaneously toxic fluid produced by mixing amygdaline and emulsine *in vitro*, therefore can be understood.

This experiment, essential to the theory of anaphylaxis, has been repeated by Friedemann, Friedberger, Biedl and Kraus, and by Briot. It is already classical.

The new toxic substance resulting from the combination of toxigen with antigen must be named, and I have suggested the word *apotoxin* derived from toxin. Friedberger has since suggested *anaphylotoxin.*

It is clear that the phenomena of anaphylaxis are those of intoxication. The poison is a special substance the source of which, combination of toxigen and antigen or toxin, we know ; the chemical reaction being :

Toxigen + antigen (toxin) = apotoxin.

Friedberger conducted one very important experiment. Starting with the idea, suggested by Marfan in 1905, that the anaphylactic poison is a precipitin, he obtained, by reaction between antigen and a serum rich in toxigen, a precipitate which he collected. *This precipitate is toxic* and induced anaphylactic phenomena. Further it combines with the complement of normal serum to which it has been added and its toxicity is thereby further increased.

Anaphylaxis, in its main feature, can be thus explained :

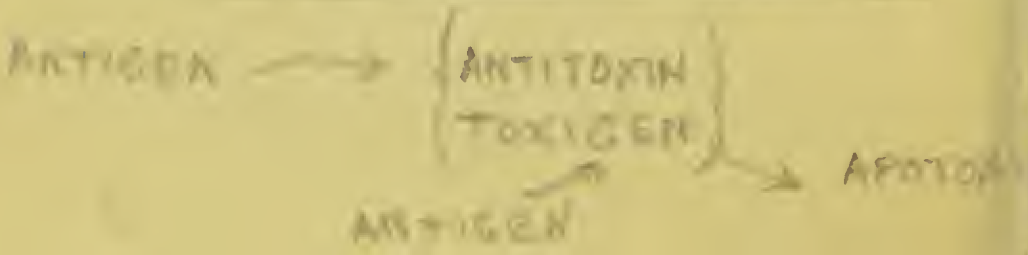
1. Formation of a toxigen, in the blood or cells, at the end of a period of incubation of ten to forty days ; and its persistence for a very long time.

2. Formation of a toxic apotoxin or precipitin as the result of interaction between the toxigen and antigen, the toxicity of which is further increased by combination with the alexin of the blood.

While these are the essential points,

other very important facts must also be referred to.

Firstly the quantity of antigen injected may be extraordinarily minute (Rosenau and Anderson). The anaphylactic state may be induced by a dose of 0·000,001 gramme of serum. Wells found that 0·000,000,05 gramme, that is the thousandth part of half a milligram, was sufficient to induce it in guinea-pigs. This minute quantity, which in addition is oxidised and rapidly destroyed when within the organism, can hardly give rise directly to the toxigen; but by stimulating the cells of the organism it leads to its production. We are entirely ignorant of how it is that an antigen forces the organism to furnish the corresponding antitoxin. We must attribute to the living cell an extraordinarily delicate and complex chemistry which supplies, by reaction with the antigen, an appropriate and special antitoxin and an appropriate



and special toxigen : for the formation of antitoxins and toxigens are parallel processes ; and it can be easily demonstrated that the blood of animals which have been given an antigen contains at the same moment a special toxigen and a special antitoxin. The specificity of antitoxic reactions, as of anaphylactic reactions, is practically absolute, though any exciting heterogeneous injection whatever, given in strong dose, has a greater effect on anaphylactised than on normal organisms.

Anaphylaxis can be produced by alimentary ingestion with difficulty. But it has been produced in definite instances by this means (Rosenau and Anderson). Likewise it has been shown that it is transmitted by heredity, and that it persists a very long time.

If these different facts, increased and not rigorously specific sensitivity, the hereditary transmission of anaphylaxis, its occasional production by ingestion, its persistence, are collated an explanation is found of what was formerly called idiosyncrasy, the peculiar sensitivity of each individual to toxic actions.

Just as we have a *psychic* personality by which each is himself and not another; so we have a *humoral* personality which also makes each different from another: this latter personality is due absolutely to the multiple ingestions and intoxications which have altered each of us by leaving indelible effects.

It is practically impossible to carry the study of apotoxins and toxigens further. Very probably there is a whole series of special toxigens and consequently of special apotoxins. Nevertheless the symptomatology of anaphylaxis remains uniform. No matter what the injected exciting substance may be or how mildly it induces anaphylaxis, the symptoms are almost the same, so that the various toxigens are probably derived from very similar if not identical substances and the various apotoxins are also derived from extremely similar if not identical substances.

Some confirmation of the theory that a toxigen reacts on the antigen is given us by a study of the doses producing anaphylaxis. The effect is not intensified by augmenting the exciting dose. For example a lightly anaphylactised animal gives an anaphylactic reaction on being injected with one part of the exciting injection; but two, three, four, or ten parts of the exciting substance may be administered and the reaction will not be increased. Moreover it occasionally happens that recovery takes place while the exciting injection is being given. These results suggest that the entire quantity of toxigen present in the animal has been neutralised by the quantity of antigen injected. In fact there is no more free toxigen in the blood and therefore no further anaphylactic reaction can be produced no matter what amount of the exciting substance is injected.

In other words, the anaphylactic reaction is determined by the quantity of toxigen present in the organism of the animal receiving the injection; and, following a small amount of the exciting substance, it will be maximal from the beginning and independent of the dose of the injected exciting substance.

What is called the anaphylactic shock, that is to say the sudden morbid onset which is rapidly recovered from and is not repeated when the exciting dose is augmented, is neither a shock nor a conflict between the injected substance and living protoplasm; it is simply the exhaustion of the toxigenic substance which is not present in unlimited amount and is immediately used up by combination with the exciting substance.

Up to the present albuminoids, chiefly colloids, have provided the antigens capable of developing anaphylaxis. Although this is a well-established fact, it is merely well-established at the present time and it is impossible to foretell the surprises of the future, more especially since Wells already has been able to inject as an anaphylactising antigen a crystalloid substance extracted from albumen, and since possibly others of a non-albuminous nature will be found capable of yielding antitoxins and toxigens.

Arthus' discovery in 1903 of the anaphylactising action of sera induced many to pursue the study of sera in *sensitising* and *exciting* injection. But it has been discovered beyond doubt that the preparatory substance and the exciting substance are not identical (Gay and Southard; Vaughan and Wheeler). My own work on the duality of the actino-congestines confirms the fact. *The sensi-*

tising substance is not always the same as the exciting substance. The two substances, it is true, are found together in the animal and vegetable fluids we use. But they are no less often dissociable either by alcohol or by heat. Although clearly further studies must still be made, it is evident that the preparatory substance is not always exciting nor is the exciting substance always preparatory. The imperfections of our chemical processes of separation allow us to suppose that separation is never complete, but we may look forward to the time when it will be possible to separate them accurately from each other.

Besredka's important work on anti-anaphylaxis, foreseen by Rosenau and Anderson, makes some of the essential points in the theory of anaphylaxis clear. He showed that anaphylaxis can be avoided by continuing the injection of the antigen in weak doses during the incubation period, which suggests that the simultaneous presence of antigen and antitoxin is impossible. My explanation of this remarkable phenomenon is that antigen and toxigen combine. As the toxigen is produced it combines with the antigen, and, if the antigen is injected in very small quantities, the resultant poison apotoxin is in too small quantity to exercise any appreciable toxic action. As the apotoxin is rapidly destroyed, which is proved by all experiments on the duration of acute anaphylaxis, it cannot accumulate in the blood, hence repeated injections of antigen in weak doses are equivalent to the destruction of toxigen and consequently lead to anti-anaphylaxis.

All the symptoms of anaphylaxis show that they are essentially the result of an acute intoxication of the nervous system. This is the conclusion I came to at the very beginning of my work in 1902 on noticing the fall in the arterial blood pressure, the mind-blindness, the motor incoordination, and the coma which follow the administration of the exciting injection in dogs.

Apparently this is the universally accepted opinion to-day, since Besredka and Roux have proved that acute anaphylaxis does not take place in an anæsthetised animal, and since I was able to demonstrate, if not always, at least sometimes, the presence of a toxigen in the cerebral tissue capable of acting on the antigen *in vitro.* Lewis and Auer suppose that there is some action on the smooth bronchial muscles. Biedl and Kraus believe there is some action on the vasomotor nerve terminations. It is possible, even likely, that such effects do occur, but they do not alter the fact that the essential feature is a very intense intoxication of the central nervous system. Four definite degrees or phases can be described, especially in the dog:

1. *Mild* anaphylaxis, characterised by pruritus and congestion of the nasal and intestinal mucosa.

2. *Moderate* anaphylaxis, characterised by vomiting, diarrhœa, motor inco-ordination, general muscular weakness with increased frequency of respiration, a semi-dyspnœic state, and a slight fall in temperature.

3. *Intense* anaphylaxis, characterised by coma, muscular inertia, complete insensibility, mind-blindness, dyspnœa almost amounting to asphyxia, and very great lowering of the arterial blood pressure.

4. *Fulminating* anaphylaxis, characterised by rapid death occurring within a few minutes; asphyxia, syncope, and immediate cessation of all activity of the nervous system.

Mention may be made here of *chronic* anaphylaxis. The symptoms of anaphylaxis generally disappear quickly. If the onset is sudden, the disappearance of the symptom is also sudden. But though the symptoms soon cease, there remained in some cases irreparable cellular lesions, for example intestinal hæmorrhages or lesions of nerve-cells of such a nature that the *restitutio ad integrum* is but brief, the animal succumbing at the end of two or three days to lesions produced at the beginning of the anaphylactic shock.

Then there is *local* anaphylaxis—that is to say, the action of the antigen does not merely affect all the cells of the organism but more especially the cells in the immediate neighbourhood of the site of injection. It may be asked whether it takes effect only on the neighbouring nerve-cells or on all cells.

The domain of anaphylaxis is immense, particularly so since study of its reactions shows incessant variability of organisms. It is, according to Doerr, a reaction of

immunity, using the word in its fullest sense, not only of phylaxis or protection but also of anaphylaxis—that is to say, contra-protection and increased sensitivity.

Now the absorption of antigens by such paths as the gastro-intestinal system is not normal, for albuminoids do not enter the circulation in their normal state when they have been modified and transformed by the gastric juices; they then cease to be antigens. The absorption of albuminoids, unaltered by digestion, modifies the living cell in a permanent manner, by increasing its vulnerability (anaphylaxis), or by diminishing it (antitoxis) or by simultaneously exercising both these contrary functions. But this cellular modification is not made directly; it is carried out by means of intermediate substances (toxigens or antitoxins) which the antigen compels the living cell to secrete. These toxigens and antitoxins, whether they circulate in the blood or become fixed in the cells, create a special humoral state for each organism, according to the antigen it receives. They constitute the individuality of beings. Possibly some day, when we shall have thoroughly studied *general* physiology and the physiology of *species*, we shall be able to consider the physiology of *individuals* which has not even been outlined yet.

It may be asked how anaphylaxis can be reconciled with the law of defence of organisms : for after all defence is diminished when sensitivity to intoxications is increased.

Now, although it can only be an hypothesis, it may be allowed that the defence of the organism is not merely a defence of individuals but also a defence of the species. It is not merely a question of each individual maintaining its existence, it is also necessary that the individuals shall remain like to each other. If heterogeneous substances can penetrate the organism with impunity and modify its fundamental chemical properties, entering into the protoplasm and altering its nature, then all would be over with the somatic constitution, the fruit of slow and ancestral acquisition, of each kind of animal. All progress acquired by selection and heredity would be lost and we should be at the mercy of chance, of accidents, and the occurrences of each day which would be capable of modifying, in accordance with complicated formulæ, the actual *optimum* state in which we are. *Every being must be stable* and it is to maintain this stability that the individual reacts with such energy to the chemical changes which affect it.

In the guinea-pig's optimum state the sera of rabbits and dogs may not replace its serum, and there is a violent reaction when, for the second time, its chemical individuality as a guinea-pig is threatened.

There is nothing to fear from crystalloid poisons which are rapidly eliminated after absorption into the blood and tissues; but in the case of those albuminoid poisons which remain in the cells and are not eliminated, there would be danger to the individuality of the species in the fact of their not remaining chemically identical.

Although these general biological considerations have not been previously presented it seems to me necessary to place them before the learned for reflection; for from a physiological point of view, it can hardly be supposed that living beings possess functions which are useless to them.

Anaphylaxis is no less important from a practical point of view. Ingenious applications of it have been made to forensic medicine and very probably these will be largely extended in the future. But it is especially in the diagnosis of disease that its greatest usefulness will lie. The diagnosis of latent tubercle by tuberculin is briefly an anaphylacto-diagnosis and the time can be foreseen when it will be possible to diagnose cancer, syphilis, hydatid, and pneumococcal infections by anaphylactic reactions.

The explanation of many morbid phenomena is imminent and we shall be able to account for many of the uncertain facts of pathology. All this can only be foreseen.

Then, as serotherapy has become so general and tends to be applied to the treatment of a large number of diseases, it is very evident that exact knowledge of serum disease, otherwise called serum anaphylaxis, is necessary. We cannot wholly neglect the accidents which may ensue upon the administration of a second serotherapeutic injection: several grave and some fatal cases are already reported. The systematic analysis of anti-anaphylactic processes will prevent these. So that from the point of view of practical medicine, as well as from the point of view of general biology, anaphylaxis seems to be a phenomenon of great importance.

But we cannot conceal the fact that, in spite of much definite knowledge there still remain many very obscure points with regard to it. Of course, science will elucidate them, but hasty generalisation must be guarded against; for, in the story of anaphylaxis as in the story of immunity, the facts, with their innumerable complex details, are incoherent, isolated, incongruous, and variable. It would be better to consider them in this light, than to desire to make them all take part in one and the same finite law and give an artificial and strained unity to what are, in the nature of things, dissociated and diverse.

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